FUNCTIONALISED AZETIDINES

A study of their synthetic accessibility and application in asymmetric synthesis

Peter Hermsen

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Nur wer der Minne entsagt,
nur wer der Liebe Lust verjagt,
nur der enzielt sich den Zauber,
zum Reif zu zwingen das Gold.

(Only he who forswears love's power,
only he who forfeits love's delight,
only he can attain the magic
to fashion the gold into a ring)

Richard Wagner
Scene 1, ' Das Rheingold '

Voorwoord

Met het schrijven van dit voorwoord nadert mijn proefschrift zijn voltooiing en komt het einde in zicht van een fantastische periode die, inclusief mijn studententijd, ruim 10 jaar heeft geduurd. In tegenstelling tot het klassieke beeld van de wereldvreemde, solitaire wetenschapper heb ik deze periode, in het bijzonder de laatste 4 jaar, in aanwezigheid van een grote groep mensen doorgebracht, welke, elk op hun eigen wijze een bijdrage hebben geleverd aan het in dit proefschrift beschreven onderzoek. Het is een academische traditie om in het voorwoord deze mensen voor het voetlicht te halen en hen op gepaste wijze te bedanken voor hun bijdrage. Dit is een uitstekende traditie waar ik mij van harte bij aansluit.

Op de eerste plaats gaat mijn dank uit naar mijn promotor Prof. Dr. Binne Zwanenburg. De afgelopen 4 jaar heeft hij mij de unieke kans geboden om mij te ontwikkelen, niet alleen als chemicus maar vooral ook als mens. De twee onvergetelijke studiereizen naar respectievelijk Zuid-Afrika en Australië hebben hierbij een essentiële rol gespeeld !

Zonder de dagelijkse discussies met Bertus Thijs zou dit proefschrift er ongetwijfeld heel anders hebben uit gezien. Bertus, jouw oprechte belangstelling, goede ideeën, vrijwel onuitputtelijke experimentele kennis, maar vooral je motiverende woorden als het weer eens niet lukte, zijn van onschatbare waarde geweest. Ik zal ze (je) missen.

Een bijzonder woord van dank verdient Dr. Ton Klunder. Ton, onze wegen kruisten elkaar voor het eerst in 1992 toen ik als aankomend organisch chemicus koos voor een hoofdvakstage in jouw groep. Vanaf het directe begin heb jij het in mij aanwezige potentieel onderkend en mij vervolgens de gelegenheid geboden om vrijwel zelfstandig onderzoek te doen. Terugkijkend, is deze periode ontzettend belangrijk geweest. Niet alleen heeft jouw onuitputtelijke enthousiasme mij definitief voor de organische chemie doen kiezen, maar de geboden vrijheid heeft me tevens optimaal voorbereid op hier beschreven promotieonderzoek. Ook tijdens dit onderzoek ben je belangstelling blijven tonen en onze vele discussies hebben wezenlijk bijgedragen aan de voltooiing ervan !

Het doen van een promotieonderzoek gaat vaak gepaard met het begeleiden van hoofdvakstudenten en/of HBO-staigaires. Ik ben in de gelukkige positie dat ik zowel twee hoofdvakstudenten, één HBO-stagair als ook een Erasmus student heb mogen begeleiden, welke in staat waren zeer zelfstandig onderzoek te doen. Patrick, dankzij jouw nimmer aflatende inzet en doorzettingsvermogen heeft ons, vaak frusterende, werk aan gefunctionaliseerde azetidin-3-onen geresulteerd in drie hoofdstukken. Roy, zonder jouw uitstekende onderzoek naar de asymmetrische ammoniolyse, was het werk dat beschreven staat in hoofdstuk 5 onmogelijk geweest. Mauro, although your work has not been included in this thesis, I would like to thank you for your contribution. Although your stay in Nijmegen was only brief, I enjoyed having you around. Sjef, jij deed je intrede in het laboratorium op een moment dat het er echt op aan kwam en je hebt me niet teleurgesteld. Verre van dat. Jij voldoet exact aan de omschrijving van de chemicus als *creatieve chaoot* welke volgens geheel eigen, en vaak onnavolgbare, regels denkt. Hoewel dit de samenwerking niet altijd even gemakkelijk maakte, heeft dit wel geresulteerd in een compleet hoofdstuk. Ik ben blij dat je me ook tijdens de promotieplechtigheid bij wilt staan !

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Dr. René de Gelder bedank ik voor de snelle structuuropheldering van de twee azetidines in hoofdstuk 3, waardoor het hele verhaal, vlak voor het einde van mijn promotieonderzoek, toch nog in elkaar bleek te passen. Gerjan Kemperman, bedankt voor je hulp bij het genereren van de PLUTON plaatjes.
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Peter

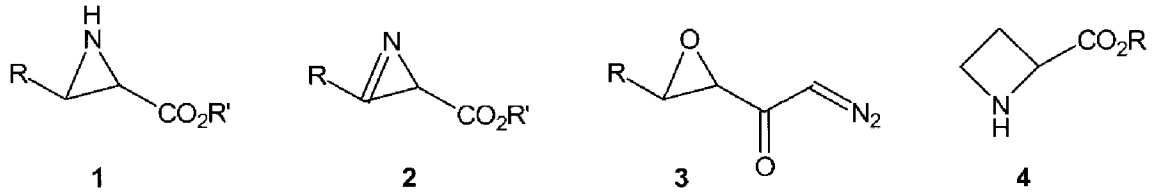
CONTENTS

1 General Introduction

1.1 Introduction

During the last three decades the research team 'Explorative Organic Synthesis' of the Department of Organic Chemistry of the University of Nijmegen has been actively engaged in the synthesis and application of functionalised small-ring heterocycles[1]. In the beginning period, the focus was mainly on three-membered ring compounds, such as aziridines **1**[2], azirines **2**[3] and epoxy diazomethyl ketones **3**[4]. Since the early 1990s however, the interest has been extended to four-membered ring compounds, especially azetidines **4**[5].

Figure 1 *Functionalised small-ring heterocycles*



The intrinsic high reactivity of small-ring heterocycles, which is associated with their highly strained structures, is one of the main reasons for the interest in this type of molecules. The synthetic potential of these small-ring heterocycles is very attractive as it allows the synthesis of a variety of natural products in a stereocontrolled fashion[4c-e], the preparation of various interesting non-proteinogenic amino acids[6] and the access to new ligands for catalytic systems. Besides the inherent ring strain of these heterocycles which makes them synthetically challenging, also their conformational rigidity is an important property in designing successful chiral auxiliaries for asymmetric synthesis.

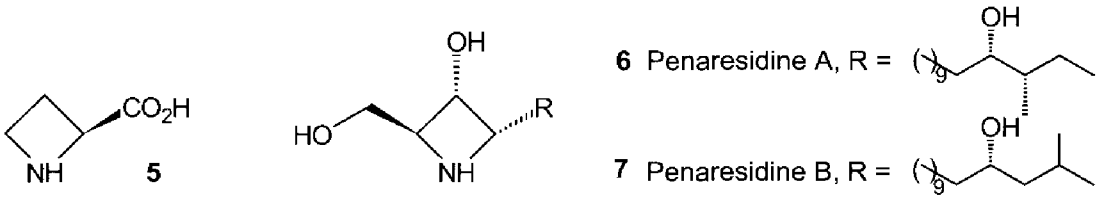
This thesis deals with functionalised azetidines with special focus on the synthetic accessibility and application as synthon and chiral auxiliary in asymmetric transformations. Since the properties and synthesis of functionalised azetidines has

been reviewed comprehensively[7], the chemistry of relevant azetidines will only be briefly discussed in the sections that follow.

1.2 Synthesis of functionalised azetidines

Since the first preparation in 1888, by the base-induced cyclisation of γ-bromo propylamine[8], azetidines have received a gradually increasing attention[7]. Especially the discovery of several biologically active functionalised azetidines, *e.g.* the non-proteinogenic amino acid azetidine-2-carboxylic acid **5**[9] and the marine metabolites Penaresidine A **6**, and B **7**[10], which identified azetidines as a potential pharmacological structural motif, stimulated the interest in these molecules[11]. Despite this fact, the synthetic methodology for the preparation of functionalised azetidines has remained underdeveloped, especially in comparison with their three and five-membered ring analogues. As a result, these diminutive heterocycles are still rather difficult amines to synthesise, especially in an enantiomerically pure form. This is illustrated by the often long and complex synthetic routes towards naturally occurring azetidines, that have been published over the years[12].

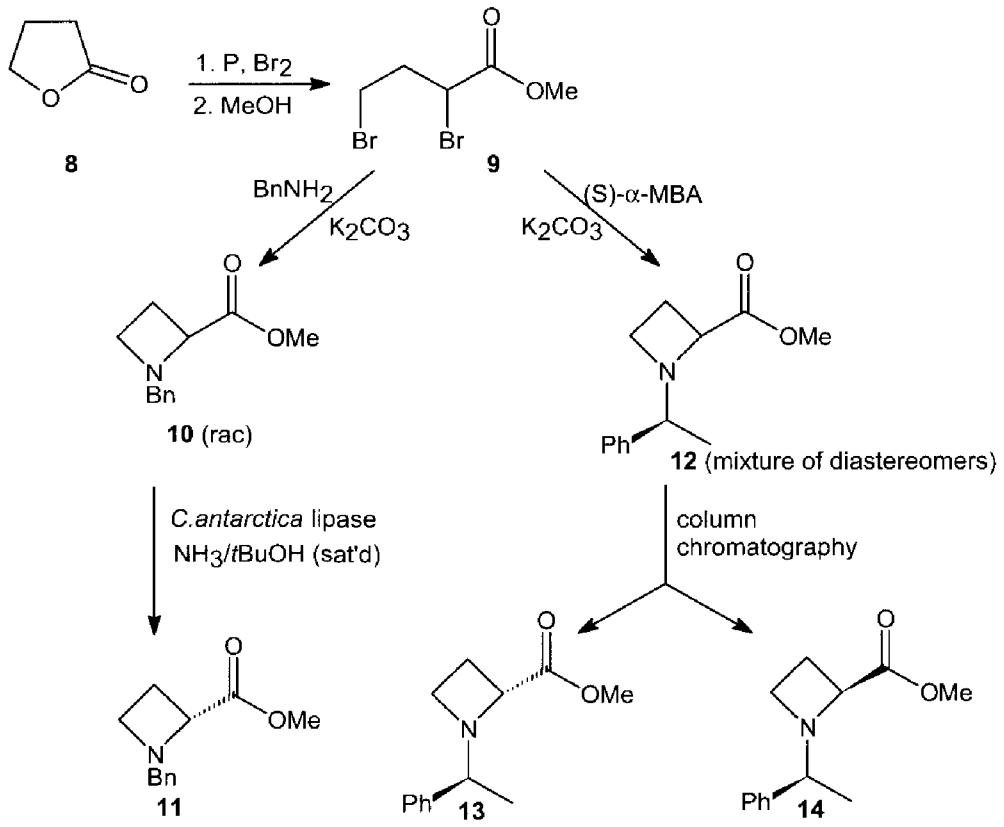
Figure 2 *Some naturally occurring azetidines*



It is relevant to mention that the envelope structure of azetidines is a unique conformation which introduces special effects between substituents at different carbon atoms. This phenomenon also plays a role in the synthesis of these four-membered ring compounds, especially when ring closure reactions are involved.
So far, the research in the Nijmegen team has primarily been concerned with the preparation of *N*-substituted azetidine-2-carboxylic esters. This has resulted in the development of a concise and efficient synthesis of this class of functionalised azetidines (Scheme 1). Reaction of γ–butyrolactone with bromine leads to 2,4-dibromobutanoate **9**. Ringclosure of this dibromide **9** with benzylamine under basic conditions, gives methyl *N*-benzyl-azetidine-2-carboxylate **10** as a racemate in moderate yield. Ammoniolysis using *Candida antarctica* lipase in ammonia saturated *tert*-butyl alcohol, selectively converts the (*S*)-enantiomer into the corresponding amide, from which the remaining (*R*)-ester **11** can easily be separated[5a,c]. Similarly,

treatment of **9** with optically pure (*S*)-α-methylbenzyl amine and subsequent chromatographic separation of the diastereoisomeric esters, gives the desired (*S,R*) and (*S,S*) methyl *N*-methylbenzyl azetidine-2-carboxylates **13** and **14** in an enantiopure form[5a,b].

Scheme 1 *Synthesis of N-substituted azetidine-2-carboxylic esters as developed in Nijmegen*



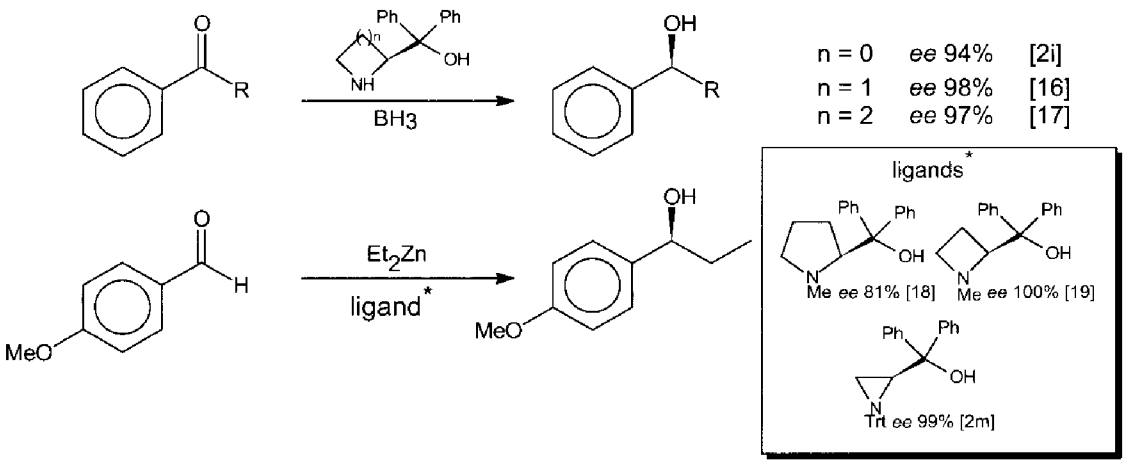
1.3 Synthetic application of functionalised azetidines

The unique envelope type rigid conformation of azetidines constitutes the main basis for the interest in these four-membered heterocyclic rings as chiral auxiliaries in (catalytic) asymmetric synthesis. It is well documented that conformational rigidity is a prerequisite for obtaining an effective and efficient auxiliary in chirality transfer reactions[13].

The basic concept of asymmetric synthesis is relatively simple. The prochiral centre in the substrate is brought into reaction with a reactant in a stereochemically well-defined environment containing one or more stereogenic centres. The reaction then takes place *via* two diastereomeric transition states whereby there is energetic preference for one of the two, leading to unequal proportions of the two enantiomeric products. The relative energy differences between the conceivable

transitions states are very small, in the order of a few kcal/mole[14]. As a consequence subtle structural changes in the stereochemical environment around the reaction centre may have a profound effect on the stereoselectivity. Structural effects may be due to steric repulsion, stereoelectronic effects, dipole-dipole interations *etc.* In actual practice the development of effective and efficient chiral auxiliaries to achieve high selectivities therefore is very difficult. As already mentioned, the energy differences are very small and seldom can be reliably calculated. Conformational rigidity as present in small-ring heterocycles is beneficial in obtaining better defined transition states and thus a better discrimination between diastereomeric transitions states as the number of conceivable transition states is reduced. There is substantial evidence that chiral auxiliaries containing the five-membered pyrrolidine ring can be successfully applied in asymmetric synthesis[15]. It should be noted that many of these pyrrolidine-type auxiliaries can readily be obtained from the relatively inexpensive and abundantly available amino acid proline or derivatives thereof. Functionalised aziridines, the three-membered rings counterparts, are at least equally effective as the pyrrolidine derived auxiliaries, although the number of examples is rather limited so far. Functionalised azetidines due to their special conformation may be excellent candidates as chiral auxiliary in asymmetric synthesis. Earlier experiments indicate a great promise for these four-membered rings. Two illustrative examples of effective use of small-ring heterocyclic amines in asymmetric synthesis are depicted in Scheme 2. Both in the borane reduction of ketones and the diethylzinc addition to aldehydes the asymmetric induction is very high for the three-, four- and five-membered ring diphenylmethanols. In the latter example the smaller-ring ligands clearly outperform their five-membered ring analogue, illustrating the positive effect of conformational rigidity on the efficiency of chiral auxilaries.

Scheme 2 *Application of functionalised small-ring heterocyclic auxiliaries in asymmetric synthesis*



Small-ring heterocylces can also be used as synthon in synthetic operations of which numerous examples are reported. However, the use of four-membered ring synthons is much less frequently encountered than that of the corresponding three[1,4c-e]- and five membered compounds.

1.4 Outline of the thesis

The research described in this thesis deals with the two main aspects mentioned in the preceding sections, *viz.* synthesis of azetidines and their use as auxiliary in asymmetric synthesis. The first part (chapters 2 and 3), describes the development of a new synthetic methodology for the preparation of di- and tri-substituted azetidines from readily available starting materials. In chapter 2, the synthesis of 2-substituted azetidin-3-ones from α-amino acids is reported. In chapter 3, these oxygenated heterocycles are then considered as intermediates in the synthesis of poly-substituted azetidines. In chapter 4, azetidines are investigated to achieve a ring extension reaction by employing the oxidative Baeyer-Villiger reaction to produce 1,3-oxazolidin-5-ones which may serve as chiral glycine equivalents. The final two chapters (chapters 5 and 6) deal with the application of functionalised azetidines as chiral auxiliary in asymmetric synthesis. In chapter 5, the enantioselective diethylzinc addition to aldehydes catalysed by functionalised azetidines is reported. Chapter 6 is devoted to the diastereoselective addition of sulfur nucleophiles to chiral methacrylic amides, derived from C_2-symmetric azetidines.

Summaries in English and Dutch conclude this thesis.

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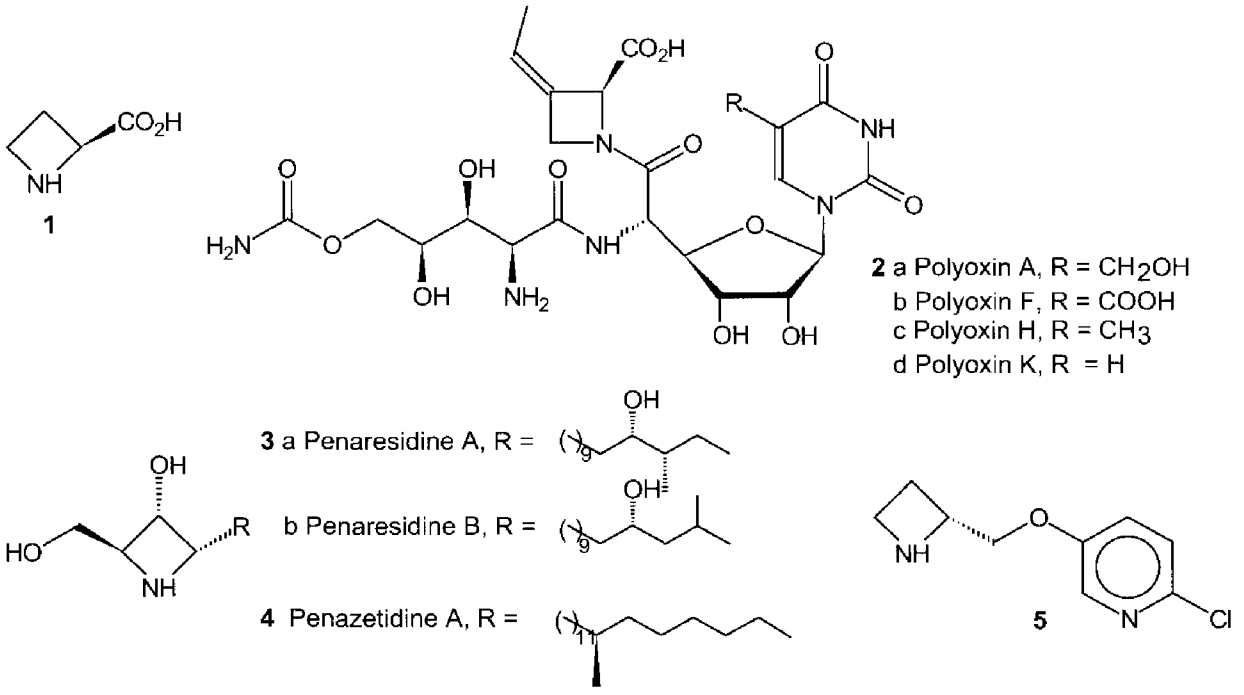
2 Synthesis of enantiopure 2-substituted azetidin-3-ones

2.1 Introduction

The isolation of azetidine-2-carboxylic acid **1** in 1956[1] and the subsequent discovery of its biological activities[2,3], has initiated an ongoing interest in both natural and synthetic functionalised azetidines. This has resulted in the identification of several other, biologically active azetidines, *e.g.* the family of the polyoxins **2**[4], nucleoside antibiotics with fungicidal properties isolated from *S. cacaoi* and more recently the sphingosine analogues Penaresidines A and B **3**[5] and Penazetidine A **4**[6]. These polyhydroxylated azetidines are marine life metabolites which exhibit potent actomyosin ATPase-activating and protein kinase C inhibiting activities, respectively.

Figure 1 *Some naturally occurring functionalised azetidines*



Being recognised as a potentially useful structural motif, azetidines have since then been included in many studies aimed at the development of new drugs, as diverse as antibacterial[7], anticonvulsant[8], antitumour[9], antipsychotic[10], anti-asthmatic[11] and antihypertensive[12] agents, immunostimulants [13], cocaine antagonists[14] and muscarine agonists[15] in the treatment of Alzheimer's disease. One of these functionalised azetidines, which has reached the stage of clinical trials, is ABT-594 **5**[16]. This surprisingly simple molecule is a powerful analgesic agent, about 30-100 times more potent than morphine in animal models, and does not seem to cause the severe side effects associated with the use of morphine, such as the development of a dependency.

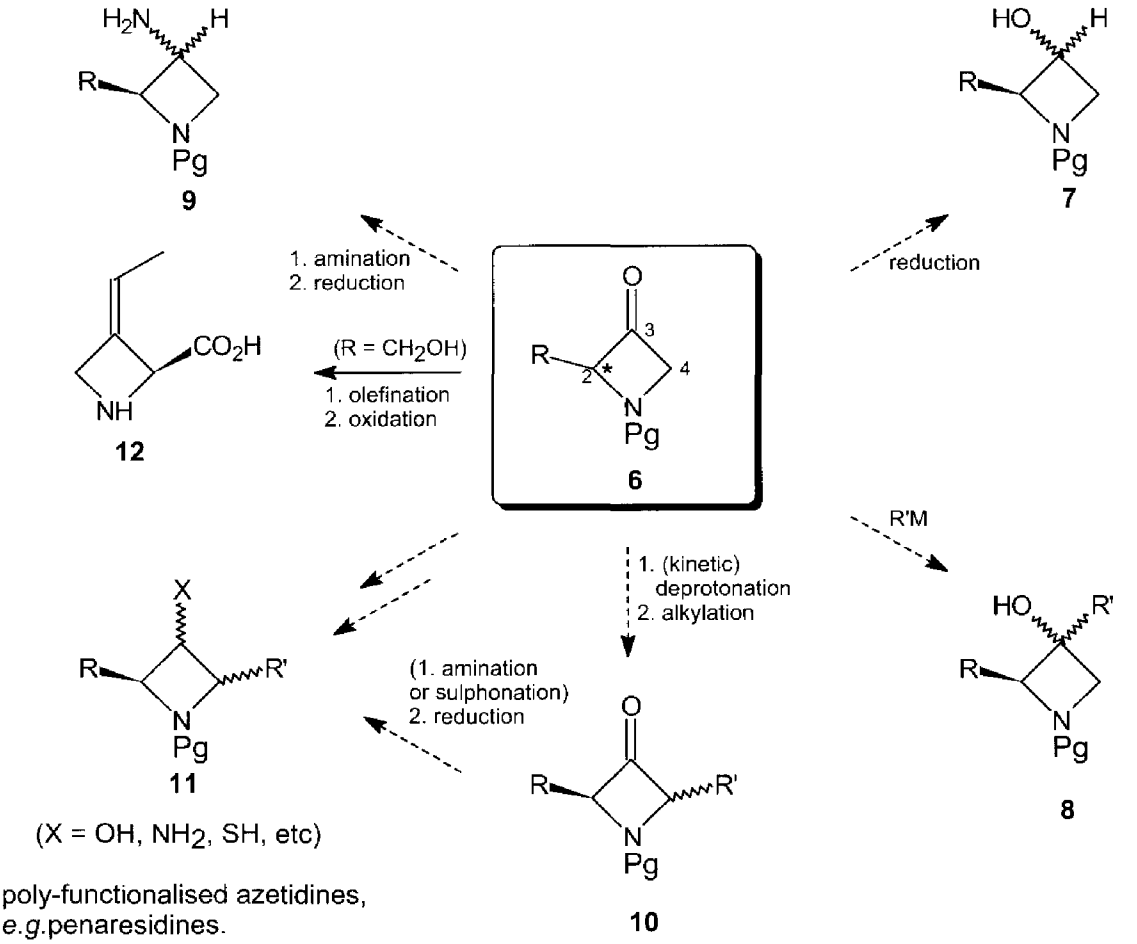
Amazingly, despite all this interest in the biological and pharmacological activity of functionalised azetidines, relative little attention has been devoted to the development of synthetic methodologies for the preparation of these molecules. Azetidines are still difficult to synthesise, especially in an enantiopure form. This is reflected by the fact that most azetidines that were included in the aforementioned pharmacological studies were either simple, achiral azetidines[7e,8-11,13,14] or racemates[7a,d,f,g,h,12,15], when they *did* contain chiral centres. Only in two studies enantiomerically pure azetidines were used. This is remarkable as it is well known that the biological activity of compounds often is dependent on their stereochemistry[17], as was confirmed by the results two of these studies[7b,c,16].

From the above it is evident that the development of drugs containing a functionalised azetidine moiety would benefit from an effective, generally applicable methodology for the synthesis of homochiral functionalised azetidines. The research discussed in this and the next chapter was aimed at developing such a methodology, based on the use of 2-substituted azetidin-3-ones **6** as four-membered ring synthons.

2.2 2-Substituted azetidin-3-ones as synthon

The choice to approach the challenging problem of developing a synthetic methodology using azetidinones as synthons, is based on the fact that this class of compounds, at least in theory, fulfils two requirements which are essential for a molecule to be useful as a chiral synthon. First of all, both enantiomers are readily available, most conveniently from α-amino acids (*vide infra*) with a wide range of substituents R corresponding to the side chain of the chosen amino acid. Furthermore, both this substituent and especially the carbonyl function at C-3 can be used as a handle for further functionalisation, enabling various transformations (Scheme 1).

Scheme 1 *2-Substituted azetidin-3-ones as synthon: some potentially interesting transformations*



The most straightforward transformations at C-3 would be reduction or alkylation, giving access to the biologically interesting[7a-c,18] 3-hydroxylated azetidines **7** and **8**. Similarly, amination of the ketone, followed by reduction or alkylation will give the equally interesting 3-amino azetidines **9**[7a-d]. These however, are just two examples of all the possible transformations as, in principle, every transformation known for (cyclic) ketones can be applied to the azetidinones **6**. Using such methodology, 3-ethylidene-azetidine-2-carboxylic acid **12** was successfully synthesised from the D-serine derived azetidine-3-one **6** (R=CH_2OH)[20], confirming the potential usefulness of **6** as a four-membered ring synthon. These transformations may be preceded by functionalisation at C-4 by means of a deprotonation-alkylation procedure, provided that the reaction conditions are carefully chosen. This will give rise to poly-functionalised azetidines **11,** *e.g.* the Penaresidines A and B **3** and Penazetidine A **4** mentioned above (Figure 1).

Several of these transformations have been achieved using simple achiral azetidin-3-ones, leading to racemic products in case a stereogenic centre is introduced during

such reactions. The usefulness of the azetidin-3-ones **6** as *chiral* synthon is determined by the question *whether* in this case these transformations will proceed with sufficient (dia)stereoselectivity. Fortunately, in the past few decades numerous successful studies have been devoted to diastereoselective transformations of optically pure 2-substituted cycloketones, *e.g.* cyclopentanones, cyclohexanones and piperidones. The limited information that is available on transformations of enantiopure 2-substituted azetidin-3-ones[21a] gives no reason to believe that the azetidinones **6** will behave significantly different when subjected to these well elaborated methodologies, suggesting that good stereoselectivities are to be expected and certainly worthwhile investigating.

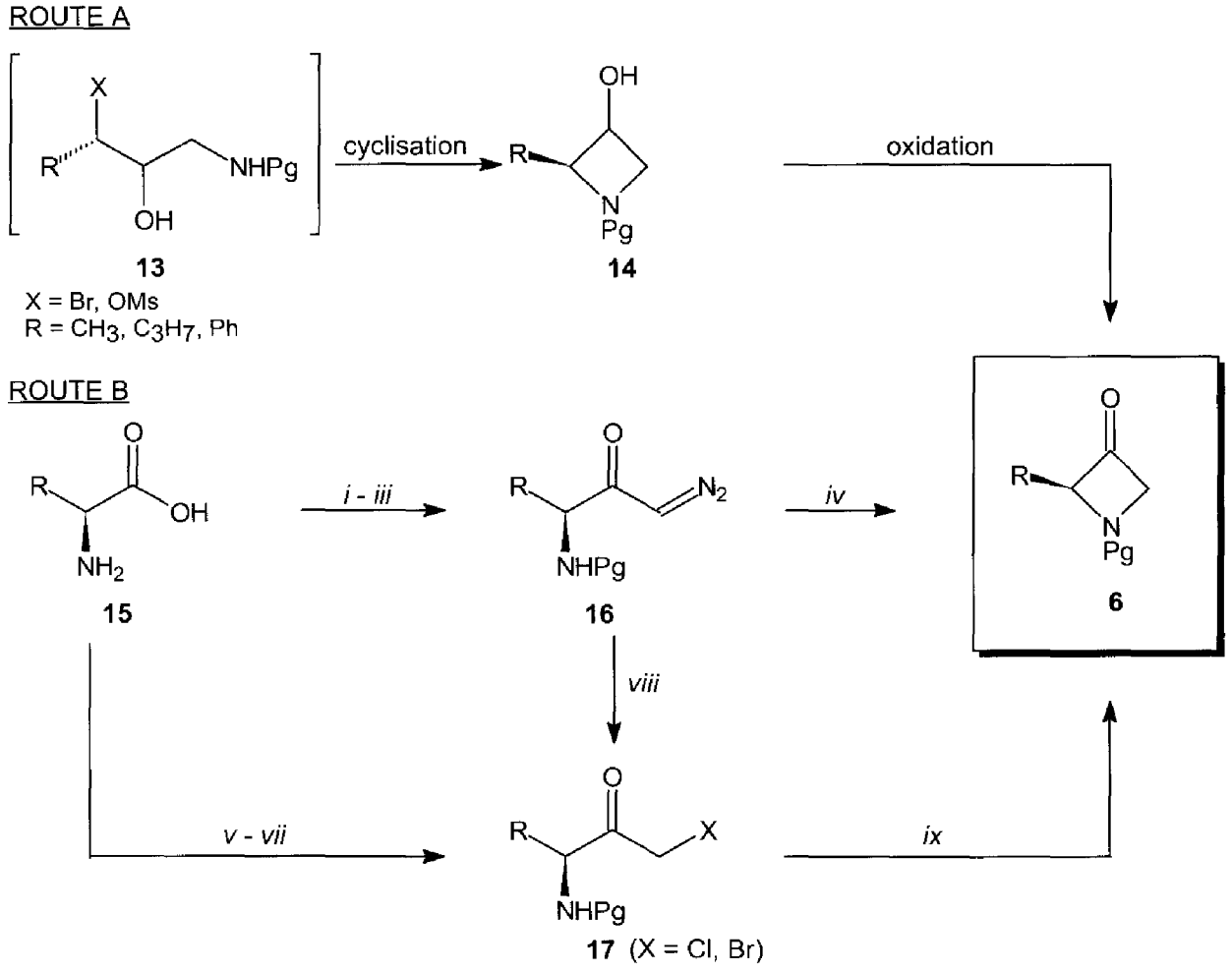
2.3 Synthesis of 2-substituted azetidin-3-ones

2.3.1 Introduction

The synthesis of azetidin-3-ones is usually achieved by the oxidation of the corresponding azetidin-3-ols **14**, using various oxidising agents, *e.g.* pyridine-SO_3[22], CrO_3/HOAc[22a,23], PDC[24], N-chlorosuccinimide[25] and $(COCl)_2$/DMSO[26]. Although this approach has mainly been used for simple unsubstituted azetidinols (R=H), the methodology can, in principle, be extended to optically pure, 2-substituted azetidin-3-ols (scheme 2, route A). A limiting factor however, is the synthetic accessibility of these alcohols. In recent years several research groups have published about this approach[7b,c,27,28], however the results are far from satisfactory. The syntheses are long, generally poor yielding and so far limited to a selected number of substituents R (methyl, propyl, phenyl, hydroxymethyl). Moreover, the sometimes harsh, oxidising reaction conditions, which also may result in considerable selfcondensation[22b], often are incompatible with sensitive functional groups present in the molecule, thus limiting the generality of this approach even further.

An alternative and better synthesis is the cyclisation of homochiral α-amino diazomethyl ketones **16** and halomethyl ketones **17** (scheme 2, route B). Both these intermediates are readily available from α-amino acids *via* a short reaction sequence. Furthermore, they can be cyclised smoothly under mild reaction conditions (*vide infra*), which are not likely to interfere with sensitive functional groups. In fact, the ease of cyclisation is unprecedented as the formation of 4-membered rings in solvolytic processes normally is highly unfavourable[29]. Hence, a facile preparation of both antipodes of a wide variety of 2-substituted azetidin-3-ones **6**, is quite feasable.

Scheme 2 *Synthetic approaches towards 2-substituted azetidin-3-ones*



i) N-protection; *ii*) activation; *iii*) CH_2N_2; *iv*) H^+, Rh(II), Cu(II) or Ag(I); *v*) esterfication; *vi*) N-protection; *vii*) CH_2ICl/LDA, CH_2Br_2/LDA/nBuLi; *viii*) HX; *ix*) $NaHCO_3$

Although both the diazomethyl ketones **16** and halomethyl ketones **17** can and have been used in this approach, the use of diazomethyl ketones is much better documented. This is not amazing, as α-amino diazomethyl ketones, being important intermediates in the Arndt-Eistert synthesis of β-amino acids[30], have been studied extensively. As a result of this, methodologies have been developed for their stereoselective synthesis from various α-amino acids[31]. Although also some α′-halomethyl ketones **17** have been synthesised from α-amino acids directly[32], they are most conveniently prepared from the corresponding diazomethyl ketones **16**[33]. However, since the diazo compounds themselves can be cyclised rather easily, there is generally no need to carry out this extra synthetic step to prepare the halomethyl ketones **17**. In addition, ring closure of diazomethyl ketones can be effected in various ways whilst the cyclisation of halomethyl ketones is limited to basic reaction conditions, which so far have only been applied to achiral halomethyl ketones[34]. Hence, the cyclisation of α-amino diazomethyl ketones is expected to be the most generally applicable and shortest route to the desired azetidin-3-ones **6**.

2.3.2 Cyclisation of α-amino diazomethyl ketones ; introductory remarks

The research published on this subject so far, falls into two categories according to the kind of nitrogen protection and methods of inducing ring closure. In the first category urethane-type of nitrogen protection is used, *e.g.* *tert*-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz), in which case the cyclisation is induced by $Cu(acac)_2$[21b] or, more successfully, by $Rh_2(OAc)_4$. This ring closure reaction proceeds *via* a carbene insertion into the N-H bond[20,21]. In the second category tosyl protection is used and the cyclisation is initiated by means of $Cu(acac)_2$[21b], $Cu(hfacac)_2$[35b], AgO_2CPh[36] or Brønsted acids, *e.g.* concentrated sulfuric acid[35a] or glacial acetic acid[35b]. In the two last mentioned cases the cyclisation proceeds *via* a cationic species.

The advantage of the first approach is that nitrogen protecting groups are used that can readily be removed under mild acidic or neutral conditions. This is an important aspect in view of the use of azetidin-3-ones as synthon for the preparation of functionalised azetidines. Unfortunately, the carbene intermediate gives rise to the formation of various by-products, with the consequence the azetidinones are usually obtained in moderate (50-60%) yield only. This, combined which the high price of $Rh_2(OAc)_4$, makes this approach less attractive, especially for multigram synthesis which is necessary when the azetidinones are to be used as synthon. The second approach does not have these problems as sulfuric acid is cheap and the cyclisation proceeds smoothly, giving the desired azetidin-3-ones in a yield of approximately 70%, depending on the nature of substituent R. However, in contrast to urethane protection, removal of the tosyl protection requires relatively harsh reaction conditions, *e.g.* sodium/naphtalene[37] or SmI_2[38], which may be impractical. It should be mentioned, however, that these harsh, radical conditions have been applied successfully as one of the final steps in the total synthesis of the sphingosines **3** and **4**[19b,d,e], indicating that tosyl protection does not necessarily need to be a serious problem.

In the ideal case however, one would like to combine the advantages of both approaches into one new synthetic methodology. Thus, combination of readily removable protecting groups with a cheap and efficient way of ring closure should be considered. The aim of the research described in this chapter was the development of a synthetic methodology for azetidinones on this basis.

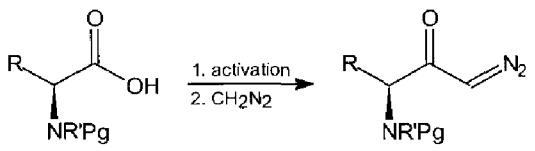
2.3.3 Synthesis of α-amino diazomethyl ketones

The study aimed at a better synthesis of azetidin-3-ones **6** was carried out with diazomethyl ketones **16**, bearing three different types of nitrogen protections groups,

viz. urethane (Cbz), benzylic (Trt, Bn) and tosyl protection. The choice of the first two protecting groups is obvious, as these groups can be removed very mildly by catalytic hydrogenolysis. The tosyl protecting group was chosen because so far, the best results have been obtained with this N-protection.

The synthesis of the diazomethyl ketones **16a-c**, **16i-p** and **16r** was readily achieved using a slight modification of literature procedures[21,31a,c]. This sequence of reactions is known to proceed without racemisation[31c,39]. After protection of the amino function using standard procedures, the acid moiety was activated by conversion into an acid chloride (tosyl) or mixed anhydride (Cbz). Subsequent treatment with ethereal diazomethane gave the diazomethyl ketones in moderate to good yields (Table 1). The synthesis of the functionalised diazomethyl ketone **16q**, derived from serine, is somewhat more laborious, because the need of protecting the side chain. For this purpose the *tert*-butyldiphenylsilyl (TBDPSi) group was chosen. This group is supposed to be sufficiently stable under the acidic conditions of the ring closure, can be removed selectively and mildly using fluoride ions and has been used previously in the synthesis of 3-ethylidene-azetidine-2-carboxylic acid **12**[20]. Thus, the synthesis of the protected amino acid derivative Ts-Ser(OTBDPSi)-OH **18q**, was achieved as follows. After conversion of L-serine into its benzyl ester[40] and subsequent tosylation, the serine derivative was treated with TBDPSiCl and imidazole in dry DMF, giving Ts-Ser(OTBDPSi)-OBn in 66% overall yield after purification by flash column chromatography. After debenzylation by catalytic hydrogenolysis the desired derivative **18q** was obtained, which was, without further purification, directly converted into the diazomethyl ketone **16q** in a manner similar to that used for the other tosyl protected diazomethyl ketones (*vide supra*).

Table 1 *Diazomethyl ketones derived from amino acids*



18a-r **16a-r**

	R	Pg	R'	cy (%)		R	Pg	R'	cy (%)
a	Me	Cbz	H	90	**i**	Me	Ts	H	66
b	*i*Pr	Cbz	H	88	**j**	Bn	Ts	H	57
c	*t*Bu	Cbz	H	90	**k**	*i*Pr	Ts	H	56
d	Me	Trt	H	58	**m**	*i*Bu	Ts	H	50
e	*i*Pr	Trt	H	--	**n**	*s*Bu	Ts	H	60
f	*i*Pr	Bn	H	--	**p**	*t*Bu	Ts	H	76
g	*i*Pr	Bnh	H	--	**q**	$CH_2OSiTBDP$	Ts	H	68
h	Me	Bn	Bn	86	**r**	CH_2CH_2SMe	Ts	H	61

In the case of benzylic-type protection the situation is somewhat more complicated. Although the synthesis of **16d** was achieved, using the same approach that was employed for the benzyloxycarbonyl protected diazomethyl ketones **16a-c**, trityl protection proved to be only feasible for this particular diazomethyl ketone. The synthesis starting from sterically more demanding amino acids, *e.g.* valine, failed, which is probably due to steric crowding around the carbonyl function making it inaccessible for diazomethane[41]. Attempts to solve this problem by choosing the acid chloride as a sterically less demanding activation were also unsuccessful, as the hydrochloric acid, liberated during reaction of the acid chloride with diazomethane, led to substantial detritylation.
As an alternative, attempts were made to prepare the diazomethyl ketones **16f** and **16g**. Both the benzyl and benzhydryl groups are also readily removable, but their reduced size as compared to the trityl group diminishes the problem of steric crowding. Unfortunately, the synthesis of both diazomethyl ketones failed, due to the still considerable nucleophilicity of the secondary amino function[42]. Activation of the thus protected amino acids **18f** and **18g** as mixed anhydride therefore resulted in spontaneous oligomerisation. Activation as acid chloride *is* possible, because the hydrochloride acid liberated in this process immediately protonates the secondary amine, thereby diminishing its nucleophilicity. However, upon addition of diazomethane the amine is liberated again, which, as before, resulted in complete oligomerisation.
In this last mentioned example, the protonation of the secondary amine can be regarded as an *in situ* protection step, the approach only failed because the 'protecting group' does not survive the conditions of the next reaction step. The use of a more stable, second protecting group at nitrogen therefore was likely to solve this problem. Indeed, dibenzylated alanine **18h** could be activated as mixed anhydride and subsequently converted into diazomethyl ketone **16h** in good yield.

All diazomethyl ketones **16** were isolated as stable, yellow solids (with the exception of **16d** which is an oil), which could be stored at low temperature for up to several months without any apparent decomposition.

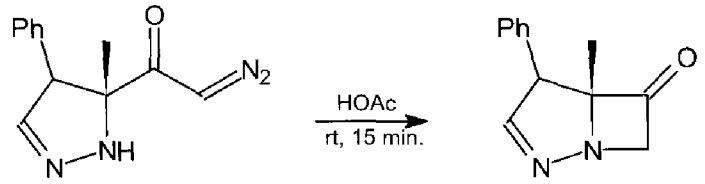
2.3.4 Cyclisation of α-amino diazomethyl ketones

Cyclisation of **16a-16c**

The most obvious approach towards a better synthesis of azetidin-3-ones would be to induce the cyclisation of benzyloxycarbonyl protected diazomethyl ketones using Brønsted acids. This method has successfully been applied for tosyl protected α-amino diazomethyl ketones[35a] (*vide supra*), and also for the efficient cyclisation of many other α-diazomethyl ketones[43]. For example, treatment of diazomethyl ketone

19 with glacial acetic acid at room temperature, gave the azetidin-3-one **20** in excellent yield[44] (Scheme 3).

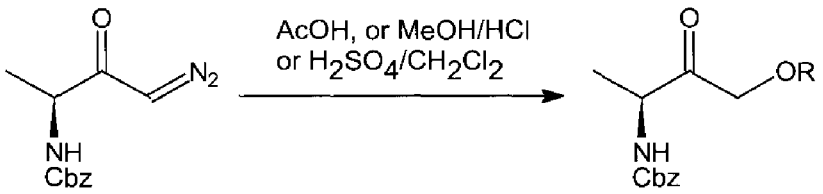
Scheme 3 *A Brønsted acid induced cyclisation*



19 **20**

Disappointingly, when diazomethyl ketone **16a** was dissolved in glacial acetic acid no apparent reaction was observed, even not after stirring for 20 hours, which underlines the stability of the α-amino diazomethyl ketones. Elevation of the temperature to approximately 100 °C a reaction *did* set in, as was evident from the evolution of nitrogen gas and simultaneous decolouration of the yellow solution. No azetidin-3-one was formed during this reaction however, as was concluded from the absence of the characteristic carbonyl absorption at 1810 cm^{-1} in the infrared spectrum. Instead, a complex mixture of polar products was obtained. Analysis of this crude mixture by means of NMR and infrared spectroscopy indicated that acetate **21a** was the major product (Scheme 4).

Scheme 4 *Acidolysis of diazomethyl ketone* **16a**



16a

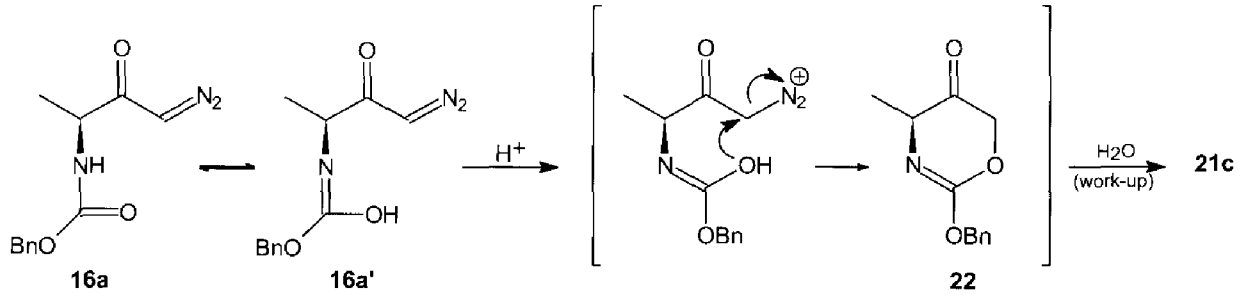
21 **a** R = Ac
b R = Me
c R = H

Similar results were obtained when **16a** was treated with catalytic amounts of hydrochloric acid in methanol[44,45] and sulfuric acid in dichloromethane[35a]. Upon addition of the acids an instantaneous and vigorous reaction took place, yielding after aqueous work-up, complex mixtures of polar products. Purification of these mixtures proved to be impossible, but analysis of the crude yields by GC/MS and NMR/IR spectroscopy indicated that **21b** and **21c** were the major respective products.

From these results it can be concluded that the secondary amino function is insufficiently nucleophilic to compete with polar, nucleophilic solvent systems (AcOH, MeOH) in the substitution reaction of the diazonium moiety. Accordingly, solvolysis is the major pathway, a side reaction which was also observed previously

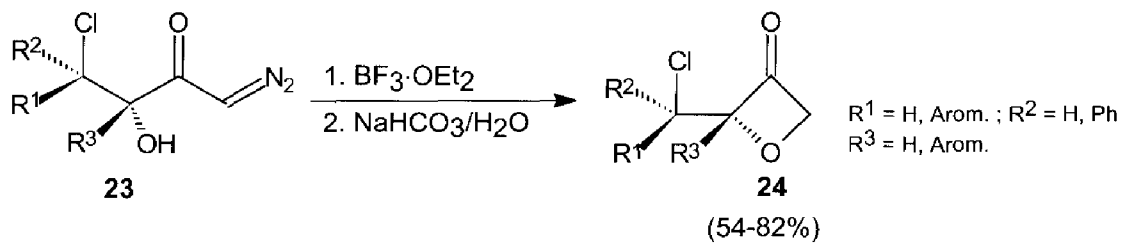
in the treatment of several tosyl protected α-amino diazomethyl ketones with excess acetic acid and sulfuric acid[35a,b]. Although the major products of the first two reactions are readily explained as arising from solvolysis, the outcome of the third reaction is less obvious. The reaction was carried out in dry dichloromethane in the presence of only two drops of concentrated sulfuric acid, therefore it seems unlikely that the rapid formation of **21c** is due to a simple hydrolysis of the diazomethyl ketone by the small trace of water present in the concentrated sulfuric acid. Instead, it seems more likely that hydroxy ketone **21c** is formed during the aqueous work-up, by the hydrolysis of an initial product **22** which is the result of an intramolecular reaction of the tautomeric amido group (Scheme 5).

Scheme 5 *Tentative mechanism explaining the formation of* **21c**



Although there is no actual proof for this mechanism, there is some evidence supporting the role of tautomerisation of **16a** in the outcome of the treatment of **16a** with sulfuric acid, namely, that tosyl protected α-amino diazomethyl ketones, which lack tautomerisation, *can* efficiently be cyclised, using the same conditions.
From previous research[46] it was known that also Lewis acids are excellent agents to induce ring closure of diazomethyl ketones. Treatment of α-hydroxy diazomethyl ketones **23** with $BF_3{\cdot}OEt_2$ gave the oxetanones **24** in excellent yields (Scheme 6).

Scheme 6 *$BF_3{\cdot}OEt_2$ induced cyclisation of α-hydroxy diazomethyl ketones*

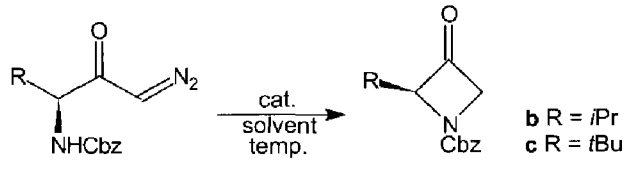


Since this cyclisation was achieved under non-nucleophilic conditions, it was hoped that Lewis acids would be suitable alternatives for the use of acetic- or hydrochloric acid in the cyclisation of **16a**. Indeed, upon the addition of a Lewis acid ($BF_3{\cdot}OEt_2$, $SnCl_4$) to a solution of **16a** an instantaneous evolution of gas is observed, indicating a

rapid decomposition of the diazomethyl ketone. Instead of the desired azetidin-3-one however, a mixture of polar products was obtained in which again hydroxy ketone **21c** again was identified as the major product. As this reaction was carried out under strict anhydrous conditions, this product can only be the result of hydrolysis during the aqueous work-up, thereby supporting the mechanism shown in Scheme 5.
The results discussed in this section show that urethane protection of amino diazomethyl ketones does not allow intramolecular nucleophilic displacement of the diazonium moiety by the amino function and is therefore not compatible with the desired, cheap manner of inducing ring closure. This implies that the synthesis of benzyloxycarbonyl protected azetidin-3-ones can only be accomplished by the transition metal induced cyclisation of diazomethyl ketones. This cyclisation proceeds *via* a carbene insertion into the N-H bond, and therefore is mechanistically entirely different from the aforementioned methods and is not hampered by the limited nucleophilicity of the amino function. However, the reactive carbene intermediate may give rise to several side reactions, *e.g.* Wolff rearrangement, insertion into other heteroatomic bonds, and makes this approach rather low yielding[21].

It is well documented that the amount and nature (metal, ligands) of the catalyst as well as the solvent can have a profound effect on both the chemo- and regioselectivity of transition metal catalysed reactions of α-diazo carbonyl compounds[47]. Some modifications of the originally published procedure were attempted, with the hope that this would lead to an improvement of the chemical yield of the cyclisation reaction (Table 2).

Table 2 *Transition metal induced decomposition of diazomethyl ketones* **16b** *and* **16c**



16 **6**

Entry	diazomethyl ketone	catalyst	amount (mol%)	solvent	temperature	cy **6** (%)
1	**16b**	$Rh_2(OAc)_4$	0.5	CH_2Cl_2	ambient	50[21]
2	**16b**	$Rh_2(OAc)_4$	1.0	CH_2Cl_2	ambient	37
3	**16c**	$Rh_2(OAc)_4$	0.5	CH_2Cl_2	ambient	53
4	**16c**	$Rh_2(OAc)_4$	6.0	benzene	reflux	13
5	**16b**	$Cu(acac)_2$	3.5	CH_2Cl_2	ambient	--[a]
6	**16b**	$Cu(acac)_2$	3.5	CH_2Cl_2	reflux	23
7	**16b**	$Cu(acac)_2$	6.0	benzene	reflux	24

[a] slow decomposition

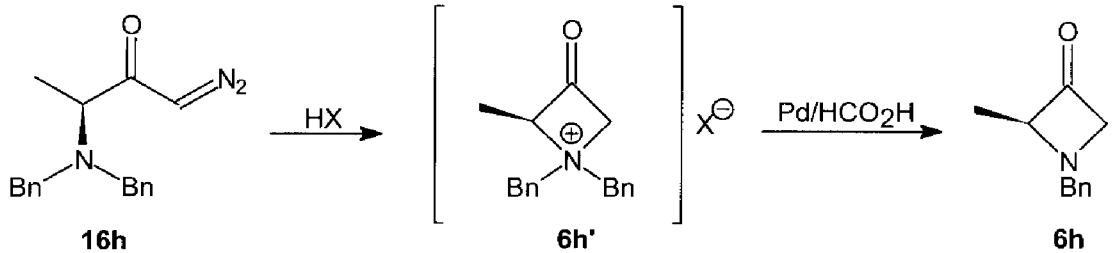
In contrast to the expectation, an increase of the amount of catalyst did not lead to an improvement of the isolated yield, but instead, the yield was significantly lower (*cf.* entries 1 and 2). A change of solvent and simultaneous elevation of the temperature, conditions previously used to synthesise benzyloxycarbonyl protected 2-methoxycarbonyl-azetidin-3-one **6** (R=COOMe)[48b], resulted in a even more profound drop in chemical yield (entry 4). The catalyst $Cu(acac)_2$ was previously successfully used in other N-H insertion reactions[48], as a cheap alternative for $Rh_2(OAc)_4$. In the present case no improvement in yield could be achieved (entries 5-7). This observation was confirmed by a recent publication[21b]. The results described above lead to the conclusion that the procedure reported by Seebach *et al.*[21a] is the best method for the preparation of benzyloxycarbonyl protected azetidin-3-ones *via* the cyclisation of diazomethyl ketones.

Cyclisation of **16d** *and* **16h**

The limited nucleophilicity of the amino function, which in the case of the benzyloxycarbonyl protected diazomethyl ketones **16a-c** prevented the acid induced cyclisation, is of no concern in the case of **16d**. The secondary amine of this trityl protected amino acid derivative is considerably nucleophilic and therefore diazomethyl ketone **16d** cyclised smoothly upon the addition of a catalytic amount of concentrated sulfuric acid, to give azetidin-3-one **6d** in 77% yield.

Unfortunately, trityl protection is limited to the alanine derived diazomethyl ketone, and benzyl protection does not allow the synthesis of the corresponding diazomethyl ketone (*vide supra*). As an alternative, dibenzyl protected diazomethyl ketone **16h** was prepared. After cyclisation the formation of an azetidinium salt **6h'** can be envisaged which, in principle, can be selectively mono-debenzylated using mild hydrogenolysis conditions[49], to give the desired benzyl protected azetidin-3-one **6h** (Scheme 7).

Scheme 7 *Attempted synthesis of benzyl protected azetidin-3-ones*



When **16h** was subjected to the standard cyclisation conditions a rapid decomposition of the diazomethyl ketone took place, yielding a very polar, salt-like product. Analysis of this product by infrared spectroscopy however, indicated that

no azetidinium salt was formed, as was deduced from the absence of the characteristic carbonyl absorption. Identification of the reaction product(s) was not possible, mainly due to severe solubility problems.

Cyclisation of **16i-16r**

The results described so far indicate that an efficient synthesis of azetidin-3-ones *via* the cyclisation of diazomethyl ketones seems to be restricted to tosyl protected diazomethyl ketones (*vide supra*). Hence, the remaining part of this chapter deals with substrates containing the N-tosyl protecting group.

Thus far, only a selected number of tosyl protected azetidin-3-ones **6** has been prepared [35,36], applying various reagents to induce ring closure, whereby sulfuric acid is most convient[35a]. The yields of these cyclisations range from 25 to 70%, depending on the nature of substituent R. The major by-product of these reactions is the α'-hydroxymethyl ketone resulting from the hydrolysis of the diazomethyl ketone under the conditions used, namely excess (2 equiv.) sulfuric acid in chloroform.

The aim of the work described in this section was twofold. First of all, the extension of the scope of this methodology by including other, both functionalised and non-functionalised, tosyl protected diazomethyl ketones. Secondly, improvement of the experimental conditions, either by reducing the amount of sulfuric acid or replacing the protic catalyst by others, *e.g.* Lewis acids. The diazomethyl ketones **16i - 16r** were used as substrates for this study (Table 3)

Table 3 *Sulfuric acid and $BF_3{\cdot}OEt_2$ induced cyclisations of diazomethyl ketones* **16i-16r**

	H_2SO_4[1]	$BF_3{\cdot}OEt_2$[1]		H_2SO_4[1]	$BF_3{\cdot}OEt_2$[1]
diazomethyl ketone	**6** (cy, %)	**6** (cy, %)	diazomethyl ketone	**6** (cy, %)	**6** (cy, %)
16i	60	88	**16n**	83	94
16j	84	95	**16p**	--[a]	97
16k	82	99	**16q**	35	95
16m	90	95	**16r**	--[a]	0

[a] not investigated. [1] Conditions : 1 mol% of catalyst in CH_2Cl_2

The data in this table clearly reveal that the use of a catalytic amount of sulfuric acid has substantial advantages over the previously applied 2 equivalents, as almost all alkyl substituted azetidin-3-ones were obtained in good yield. The use of a catalytic amount of $BF_3{\cdot}OEt_2$ however, proved to be superior, both with respect to isolated

yield and ease of work-up. Under these completely anhydrous conditions a very smooth cyclisation takes place, producing the desired azetidin-3-ones **6** as practically pure solids in almost quantitative yield without the need of column chromatography.

A more striking difference between these two acid catalysts, in terms of chemical yield, is observed in the case of the functionalised diazomethyl ketone **16q**. The use of a catalytic amount of sulfuric acid gave the desired azetidinone **6q** only in a disappointingly low yield of 35%. The major by-product of this reaction was tBuPh$_2$SiOH. In contrast, the use of $BF_3{\cdot}OEt_2$ results in a fast and smooth cyclisation, giving **6q** in excellent yield. Unfortunately, this was not the case with diazomethyl ketone **16r**, derived from methionine. Upon the addition of the Lewis acid, a spontaneous reaction took place accompanied by the formation of a substantial amount of precipitate, however, no azetidinone **6r** had been formed. In fact, no material was present in the organic layer. No reaction product could be isolated from this reaction. It may be speculated that the sulphide of the side chain reacts intramolecularly with the diazonium moiety, but no evidence for such a reaction could be obtained.

2.4 Concluding remarks

The aim of the study described in this chapter, was the development of a cheap, simple and efficient synthesis of enantiopure 2-substituted azetidin-3-ones by cyclisation of diazomethyl ketones derived from α-amino acids. The results indicate that this goal has only been achieved in part.

Urethane-type protection of diazomethyl ketones proved to be incompatible with the desired methodology to induce ring closure. Both the use of Brøndsted- and Lewis acids resulted in the solvolysis or hydrolysis of the diazo moiety, due to the limited nucleophilicity of the amino function. Intramolecular cyclisation of diazomethyl ketones having urethane-type protecting functions therefore could only be achieved by a carbene insertion into the N-H bond of the amino function. Such a cyclisation is always accompanied by several side-reactions. It was found that this cyclisation could be best performed by the method reported in the literature using $Rh_2(OAc)_4$ as the catalyst.

Cyclisation of trityl protected diazomethyl ketones *is* possible using a catalytic amount of concentrated sulfuric acid. However, trityl protected diazomethyl ketones could only be prepared from alanine. Sterically more demanding amino acids failed

to give the corresponding diazomethyl ketones. The same holds for other benzyl-type (Bn, Bnh) protected diazomethyl ketones.

The best results for the synthesis of azetidin-3-ones were obtained with N-tosyl protected amino diazomethyl ketones derived from various α-amino acids. The intramolecular cyclisation was most conveniently accomplished by using a catalytic amount (1 mol%) of BF_3-etherate in dichloromethane as the catalyst, which is a considerable improvement of existing procedures.

The chemistry of azetidin-3-ones containing various N-protecting groups will be described in the next chapter.

2.5 Experimental Part

General remarks
Melting points were determined using a Reichert thermopan microscope and are uncorrected. Optical rotations were measured with a Perkin Elmer automatic polarimeter, model 241 MC, using concentrations *c* in g/100 ml at 20 °C in the solvents indicated. ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AC 100 (100 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer. The chemical shift δ is given in ppm relative to the internal standard (TMS for ^{1}H-NMR, $CDCl_3$ for ^{13}C-NMR). IR spectra were recorded on a Perkin Elmer 298 spectrophotometer. The wavenumber ν is listed in cm^{-1}. For (high resolution) mass spectra a double focussing VG7070E mass spectrometer was used. GC-MS were measured using a Varian Saturn II GC-MS by on-column injection (DB-1 column, length 30 m, internal diameter 0.25 mm, film thickness 0.25 μm). Elemental analyses were performed using a Carlo Erba Instruments CHNS-O EA 1108 element analyzer.

Chemicals
Diethyl ether was pre-dried over calcium chloride, then distilled from calcium hydride and stored over 4 Å molsieves. THF was pre-distilled from calcium hydride, and prior to use distilled from sodium/benzophenone. Hexane, ethyl acetate and dichloromethane were distilled from calcium hydride and stored over 4 Å molsieves. All other reagents were analytic grade and used as such. Diazomethane was prepared from Diazald® as an approximately 0.3 M solution in diethyl ether. During the use of diazomethane, proper safety precautions were taken.

N-protected amino acids **18**
The *N*-protected amino acids **18a-c**[50], **18d**[51] and **18i-18p**, **18r**[52] were prepared according to standard literature procedures and used without further purification. Compound **18h** was obtained in 78% yield by dibenzylation of Ala-OMe.HCl (K_2CO_3, BnBr in methanol/water) and subsequent hydrolysis of the methyl ester. Serine derivative **18r** was obtained in 60% yield by silylation of Ts-Ser-OBn[40,52] using *tert*-butyldiphenylsilyl chloride with imidazole as the base in dry DMF[54], followed by catalytic hydrogenolysis of the ester (1 atm H_2, Pd/C, MeOH). Both **18h** and **18r** were used without further purification.

Diazomethyl ketones **16**

General procedure for the preparation of urethane- and benzyl-type protected amino diazomethyl ketones 16a-c, 16d and 16h (GP1)

Under exclusion of moisture the *N*-protected amino acid was dissolved in dry THF (~ 0.1 M) and the solution was cooled in ice. *Via* a syringe Et_3N (1.1 equiv.) and *i*BuOC(O)CCl (1 equiv.) were added and the obtained white suspension was stirred for 1 h at 0 °C. The precipitate was filtered off and an ethereal solution of diazomethane was added to the filtrate until a rich yellow colour persisted over a longer period of time (approx. 2-3 equiv.). The reaction mixture was stirred at ambient temperature for 3 h (12 h in the case of trityl protection) after which excess diazomethane was removed by flushing with nitrogen. The solution was concentrated *in vacuo* and the obtained diazomethyl ketone was purified by flash column chromatography (hexane/ethyl acetate 3:1 → 2:1 (v/v)). Analytical samples were obtained by crystallisation from hexane.

Diazo-(*N*- benzyloxycarbonyl-L-alanyl)methane **16a**
Cbz-Ala-OH **18a** (1.13 g, 5.08 mmol) was converted according to GP1 yielding 1.13 g (90%) of **16a** as a thick yellow oil which slowly solidified, mp 93-94 °C, $[a]_D^{20}$ -43.4° (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz) δ : 1.34 (d, ^3J = 7.1 Hz, 3H, CH_3), 4.29 (br s, 1H, C*H*NCbz), 5.10 (dd, J_{AB} = 14.2 Hz, 2H, CH_2Ph), 5.40 (s, 1H, COC*H*N_2), 6.00 (br s, 1H, N*H*), 7.30 (m, 5H, C_6H_5). ^{13}C NMR (100 MHz) δ : 18.4 (CH_3), 53.5 (CHN_2), 66.9 ($CHCH_3$ and CH_2Ph), 128.1 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 136.2 (C_{Ar}), 155.6 (NC=O), 193.7 (C=O). IR ($CHCl_3$) ν : 3410 (NH), 2105 (N_2), 1710 (C=O, urethane), 1635 (C=O). MS (CI) *m/z* (%) : 248(3) [M+1], 220(40) [M+1-N_2], 91(100) [C_7H_7]. $C_{12}H_{13}N_3O_3$ (247.09) calc. C 58.29 H 5.30 N 16.99 found C 58.30 H 4.74 N 16.91.

Diazo-(*N*-benzyloxycarbonyl-L-valinyl)methane **16b**
Cbz-Val-OH **18b** (10.0 g, 39.7 mmol) was converted according to GP1 yielding 9.63 g (88%) **16b** as a yellow solid, mp 70 °C, $[a]_D^{20}$ -40.2° (*c* = 1, $CHCl_3$). ^1H NMR (100 MHz) δ : 0.94 (2xd, ^3J = 7.1 Hz, 6H, $CH(CH_3)_2$), 2.04 (m, 1H, C*H*$(CH_3)_2$, 4.11 (m, 1H, C*H*NCbz), 5.10 (s, 2H, CH_2Ph), 5.39 (s, 1H, COC*H*N_2), 5.59 (d, ^3J = 8.8 Hz, 1H, N*H*), 7.34 (m, 5H, C_6H_5). ^{13}C NMR(25 MHz) δ : 17.1 and 19.1 ($C(CH_3)_2$), 30.8 ($C(CH_3)_2$), 54.4 (CHN_2), 60.1 (CH*i*Pr), 66.8 (CH_2Ph), 127.8 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 156.1 (NHC=O), 193.0 (C=O). IR ($CHCl_3$) ν : 3450 (NH), 2110 (N_2), 1720 (C=O, urethane), 1640 (C=O). MS (CI) *m/z* (%) : 248(13) [M+1-N_2], 91(100) [C_7H_7].

Diazo-(*N*-benzyloxycarbonyl-L-*tert*-leucinyl)methane **16c**
Cbz-*t*Leu-OH **18c** (4.6 g, 17.3 mmol) was converted according to GP1 yielding 4.5 g (90%) of **16c** as a yellow solid, mp 77-78 °C, $[a]_D^{20}$ -12.1 ° (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz) δ : 0.99 (s, 9H, *t*Bu), 4.00 (d, ^3J = 9.2 Hz 1H, C*H*NHCbz), 5.09 (s, 2H, CH_2Ph), 5.37 (s, 1H, C*H*N_2), 5.54 (d, ^3J = 9.0 Hz, 1H, N*H*), 7.31 (m, 5H C_6H_5). ^{13}C (100 MHz) δ : 26.7 ($C(CH_3)_3$), 35.1 ($C(CH_3)_3$), 56.3 ($COCHN_2$), 65.1 (CH*t*Bu), 67.1 (CH_2Ph), 128.1 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 136.2 (C_{Ar}), 156.2 (NC=O), 192.9 (C=O). IR ($CHCl_3$) ν : 3455 (NH), 2100 (N_2), 1700 (C=O, urethane), 1630 (C=O). MS (CI) *m/z* (%) : 262 (62) [MH^+ - N_2], 218 (15) {[MH^+ - N_2 - CO_2], 108 (100) [C_7H_7OH]. $C_{15}H_{19}N_3O_3$ (289.33) calcd. C 62.27, H 6.62 N 14.52 found C 62.35 H 6.60 N 13.73

Diazo-(*N*-trityl-L-alanyl)methane **16d**

Trt-Ala-OH (5.4 g, 16.4 mmol) was converted according to GP1 yielding 3.4 g (58%) of **16d** as a thick, yellow oil, $[a]_D^{20}$ -6.1° (*c* = 1, $CHCl_3$). ^1H NMR (100 MHz) δ : 0.95 (br s, 1H, N*H*), 1.16 (d, *J* = 6.8 Hz), 3.24 (m, 1H, C*H*CH_3), 4.89 (s, 1H, C*H*N_2), 7.17-7.51 (m, 15H, arom.). IR ($CHCl_3$) ν : 3000-2820, 2105 (N_2), 1640 (C=O). ^{13}C (75 MHz) δ : 16.9 (CH_3), 52.0 (CHN_2), 67.9 ($CHCH_3$), 75.5 ($C(C_6H_5)_3$), 127.1 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 146.8 (C_{Ar}), 204.9 (*C*=O). IR ($CHCl_3$) ν : 2110 (N_2), 1640 (C=O).MS (CI) *m/z* (%) : 243(100), 105(51) [M+1-Trt-N_2].

Diazo-(*N*-dibenzyl-L-alanyl)methane **16h**

Bn_2-Ala-OH (16.0 g, 59.5 mmol) was converted according to GP1 yielding 15.0 g (86%) of **16h** as a yellow solid, mp 100-101 °C, $[a]_D^{20}$ -203.6° (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz) δ : 1.24 (d, ^3J = 6.8 Hz, 3H, C*H*$_3$), 3.34 (q, ^3J = 6.7 Hz, 1H, C*H*NBn_2), 3.60 (dd, J_{AB} = 13.6 Hz, 4H, 2x C*H*$_2$Ph), 5.91 (s, 1H, C*H*N_2), 7.33 (m, 10H, arom.). ^{13}C (100 MHz) δ : 7.7 (CH_3), 53.1 (CHN_2), 54.3 (CH_2Ph), 61.1 ($CHCH_3$), 127.1 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 138.9 (C_{Ar}), 197.3 (*C*=O). IR ($CHCl_3$) ν : 2105 (N_2), 1635 (C=O). MS (CI) *m/z* (%) : 294(82) [M+1], 266(78) [M+1-N_2], 224(100). $C_{18}H_{19}N_3O$ (293.15) calcd. C 73.70 H 6.53 N 14.32 found C 73.70 H 5.75 N 13.41.

General procedure for the preparation of N-tosyl protected amino diazomethyl ketones 16i-16r (GP2)

Under exclusion of moisture, the N-tosyl amino acid was dissolved in dry CH_2Cl_2 (~0.5 M) and the solution was cooled in ice. Oxalyl chloride (1.1 equiv.) was added, followed by a few drops of DMF. The yellow solution was subsequently stirred for 3 h, during which the temperature was allowed to rise to ambient. The solvent was then removed *in vacuo* and the residue redissolved in dry THF. To this solution an ethereal solution of diazomethane was added until a rich yellow colour persisted over a longer period of time (approx. 2-3 equiv.). After stirring for 3 h at ambient temperature, excess diazomethane was removed by flushing with nitrogen after which the reaction mixture was concentrated *in vacuo*. The obtained, oily diazomethyl ketone was purified by flash column chromatography (hexane/ethyl acetate 5:1 (v/v)). Analytical samples were obtained by crystallisation from hexane.

Diazo-(*N*-tosyl-L-alanyl)methane **16i**

Ts-Ala-OH **18i** (10.18 g, 41.9 mmol) was converted according to GP2 yielding 6.72 g (66%) of **16i** as a yellow solid, mp 74-75 °C [lit.[31a,36] 75-76 °C], $[a]_D^{20}$ -115.6° (*c* = 1, $CHCl_3$) [lit.[36] $[a]_D^{20}$ -133° (*c* = 1, $CHCl_3$)]. ^1H NMR (100 MHz) δ : 1.23 (d, ^3J = 7.1 Hz, 3H, C*H*$_3$), 2.42 (s, 3H, C*H*$_3C_6H_4$), 3.85 (m, 1H, C*H*NTs), 5.57 (s, 1H, C*H*N_2), 5.84 (d, ^3J = 7.2 Hz, 1H, N*H*Ts), 7.29 (d, *J* = 8.1 Hz, 2H, C_6H_4), 7.72 (d, *J* = 8.1 Hz, 2H, C_6H_4). ^{13}C (75 MHz) δ : 19.6 (CH_3), 21.5 ($CH_3C_6H_4$), 53.9 (CHN_2), 55.3 ($CHCH_3$), 127.1 ($C_{Ar}H$), 129.7 ($C_{Ar}H$), 136.8 (C_{Ar}), 143.8 (C_{Ar}), 187.0 (*C*=O). IR ($CHCl_3$) ν : 3450 (NH), 2110 (N_2), 1640 (C=O), 1350 (SO_2).

Diazo-(N-tosyl-L-phenylalanyl)methane **16j**

Ts-Phe-OH **18j** (1.02 g, 3.95 mmol) was converted according to GP2 yielding 0.63 g (57%) of **16j** as a yellow solid, mp 99-100 °C [lit.[36] 100-101 °C], $[a]_D^{20}$ -93.9 (c =1, $CHCl_3$) [lit.[36] $[a]_D^{10}$ -78.1 (c=1, CH_2Cl_2]. ^{1}H NMR (100 MHz) δ : 2.37 (s, 3H, CH_3C$_6$H$_4$), 2.80 (dd, part of AB, J_{AB} = 13.6 Hz, ^3J = 7.6 Hz, 1H, CHHPh), 3.00 (dd, part of AB, J_{AB} = 13.6 Hz, ^3J = 6.1 Hz, 1H, CHHPh), 4.00 (m, 1H, CHNTs), 5.54 (s, 1H, COCHN$_2$), 5.67 (d, ^3J = 7.7 Hz, NH), 6.98 (m, 2H, C$_6H_5$), 7.18 (m, 5H, C$_6H_5$ and CH$_3$C$_6H_4$), 7.52 (d, J = 8.2 Hz, 2H, CH$_3$C$_6H_4$). ^{13}C NMR (25 MHz) δ : 21.5 (CH$_3$C$_6$H$_4$), 38.7 (CH$_2$Ph), 54.8 (COCHN$_2$), 61.0 (CHNHTs), 127.0 (C$_{Ar}$H), 128.8 (C$_{Ar}$H), 129.2 (C$_{Ar}$H), 129.8 (C$_{Ar}$H), 135.3 (C$_{ar}$), 136.4 (C$_{ar}$), 143.6 (C$_{ar}$), 192.9 (C=O). IR ($CHCl_3$) ν : 3300 (NH), 2105 (N$_2$), 1630 (C=O). MS (EI) m/z (%) : 344(28) [M+1], 316(100) [M+1-N$_2$].

Diazo-(N-tosyl-L-valinyl)methane **16k**

Ts-Val-OH **18k** (18.66 g, 68.84 mmol) was converted according to GP2 yielding 10.83 g (56%) of **16k** as a yellow solid, mp 86-87 °C [lit.[31a] 76-78 °C], $[a]_D^{20}$ -71.2° (c = 1, $CHCl_3$) [lit.[31a] $[a]_D^{20}$ -41.2° (c = 1, $CHCl_3$)]. ^{1}H NMR (100 MHz) δ : 0.86 (dd, ^3J = 6.7 Hz, 6H, CH(CH_3)$_2$), 1.95 (m, 1H, CH(CH$_3$)$_2$), 2.41 (s, 3H, CH_3C$_6$H$_4$), 3.62 (dd, ^3J = 8.8 and 4.7 Hz, 1H, CHNHTs), 5.32 (s, 1H, COCHN$_2$), 5.63 (d, ^3J = 8.8 Hz, 1H, NH), 7.28 (d, J = 8.1 Hz, 2H, C$_6H_4$CH$_3$), 7.73 (d, J = 8.1 Hz, 2H, C$_6H_4$CH$_3$). ^{13}C NMR (25 MHz) d : 16.9 and 19.2 (CH(CH$_3$)$_2$), 21.4 (CH$_3$C$_6$H$_4$), 31.4 (CH(CH$_3$)$_2$), 54.6 (COCHN$_2$), 64.7 (CHNHTs), 127.2 (C$_{Ar}$H), 129.5 (C$_{Ar}$H), 136.7 (C$_{ar}$), 143.6 (C$_{ar}$), 192.6 (C=O). IR ($CHCl_3$) ν : 3250 (NH), 2105 (N$_2$), 1640 (C=O), 1355 (SO$_2$), 1130. MS (EI) m/z (%) 268 (6) [M$^+$ - N$_2$], 155 (42) [C$_7$H$_7$SO$_2^+$], 91 (100) [C$_7$H$_7^+$], 70(78), 42 (52) [C$_3$H$_7^+$]
C$_{13}$H$_{17}$N$_3$O$_3$S (295.35): calcd. C 52.87, H 5.80 N 14.23; found C 52.89, H 5.88 N 14.09.

Diazo-(N-tosyl-L-leucinyl)methane **16m**

Ts-Leu-OH **18m** (5.67 g, 19.88 mmol) was converted according to GP2 yielding 3.75 g (50%) of **16m** as a yellow solid, mp 76-77 °C [lit.[31a] 80 °C], $[a]_D^{20}$ -62.8° (c = 1, $CHCl_3$) [lit.[31a] $[a]_D^{20}$ -78.0° (c = 1, $CHCl_3$)]. ^{1}H NMR (100 MHz) δ : 0.81 (dd, ^3J = 6.4 Hz, 6H, CH(CH_3)$_2$), 1.32 (m, 2H, C$H_2$$i$Pr), 1.71 (m, 1H, C$H$(CH$_3$)$_2$), 2.42 (s, 3H, C$H_3C_6H_4$), 3.77 (m, 1H, C$H$NTs), 5.21 (s, 1H, C$HN_2$), 5.33 (d, J = 8.8 Hz, 1H, NH), 7.29 (d, J = 8.1 Hz, 2H, C$_6H_4$CH$_3$), 7.73 (d, J = 8.1 Hz, 2H, C$_6H_4$CH$_3$). ^{13}C NMR (25 MHz) d : 21.1 (CH$_3$C$_6$H$_4$), 21.3 and 22.6 (CH(CH$_3$)$_2$), 24.1 (CH(CH$_3$)$_2$), 41.9 (CH$_2$$i$Pr), 54.0 (COCHN$_2$), 58.2 (CHNHTs), 127.1 (C$_{Ar}$H), 129.5 (C$_{Ar}$H), 136.7 (C$_{ar}$), 143.6 (C$_{ar}$), 193.7 (C=O). IR ($CHCl_3$) ν : 3300 (NH), 2105 (N$_2$), 1635 (C=O), 1350 (SO$_2$), 1100. MS (CI) m/z (%) : 327 (75) [M + NH$_4^+$]', 310 (6) [MH$^+$], 299 (100) [M + NH$_4^+$ - N$_2$], 282 (92) [MH$^+$ - N$_2$], 126 (12) [M - N$_2$ - Tos].
C$_{14}$H$_{19}$N$_3$O$_3$S (309.38): calcd. C 54.35, H 6.19, N 13.58, found: C 54.63, H 6.21, N 13.15.

Diazo-(N-tosyl-L-*iso*leucinyl)methane **16n**

Ts-Ile-OH **18n** (2.90 g, 9.99 mmol) was converted according to GP2 yielding 1.90 g (60%) of **16n** as a yellow solid, mp 82-83 °C, $[a]_D^{20}$ -56.2° (c = 1, $CHCl_3$). ^{1}H NMR (100 MHz) δ : 0.83 (m, 6H, 2x CH_3), 1.20 (m, 1H, CH(Me)Et), 1.64 (m, 2H, CH_2CH$_3$), 2.41 (s, 3H, CH_3C$_6$H$_4$), 3.64 (dd, ^3J = 8.9 and 5.0 Hz, 1H, CHNHTs), 5.23 (s, 1H, COCHN$_2$), 5.41 (d, ^3J = 8.9 Hz, 1H, NH), 7.28 (d, J = 8.2 Hz, 2H, C$_6H_4$CH$_3$), 7.71 (d, J = 8.2 Hz, 2H, C$_6H_4$CH$_3$). ^{13}C NMR (25 MHz) δ : 11.3 (CH$_3$CH$_2$), 15.5 (CH$_3$CH), 21.4 (CH$_3$C$_6$H$_4$), 24.1 (CH$_2$CH$_3$), 38.2 (CH(Me)Et), 55.0 (COCHN$_2$),

64.2 (CHNHTs), 127.2 ($C_{Ar}H$), 129.5 ($C_{Ar}H$), 136.6 (C_{ar}), 143.6 (C_{ar}), 192.6 (C=O). IR ($CHCl_3$) ν : 3310 (NH), 2115 (N_2), 1635 (C=O), 1345 (SO_2), 1100. MS (EI) *m/z* (%): 281 (5) [M^+ - N_2], 155 (38) [$C_7H_7SO_2^+$], 91 (100) [$C_7H_7^+$], 57 (44) [$C_4H_9^+$]. $C_{14}H_{19}N_3O_3S$ (309.38): calcd. C 54.35, H 6.19, N 13.58, found: C 54.45, H 6.21, N 13.18

Diazo-(N-tosyl-L-*tert*-leucinyl)methane **16p**

Ts-*t*Leu-OH **18p** (1.45 g, 5.1 mmol) was converted according to GP2 yielding 1.20 g (76 %) of **16p** as a yellow solid, mp 105-106 °C, $[a]_D^{20}$ -50.3° (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz) δ : 0.95 (s, 9 H, *t*Bu), 2.41 (s, 3H, $CH_3C_6H_4$), 3.39 (d, ^3J = 10.0 Hz, 1H, *CH*NHTs), 4.98 (s, 1H, CHN_2), 5.67 (d, ^3J = 9.8 Hz, 1H, NH), 7.27 (d, *J* = 8.2 Hz, 2H, $C_6H_4CH_3$), 7.71 67 (d, ^3J = 9.7 Hz, 1H, NH), 7.27 (d, *J* = 8.2 Hz, 2H, $C_6H_4CH_3$). ^{13}C (100 MHz) δ : 21.5 (CHC_6H_4), 26.6 ($C(CH_3)_3$), 35.5 ($C(CH_3)_3$), 59.1 (CHN_2), 67.4 (*C*HNHTs), 127.6 ($C_{Ar}H$), 129.6 ($C_{Ar}H$), 136.8 (C_{Ar}), 143.7 (C_{Ar}), 191.9 (*C*=O). MS (CI) *m/z* (%) : 327 (75) [M + NH_4^+], 299 (82) [M + NH_4^+ - N_2], 283 (100) [MH^+ - N_2]. IR ($CHCl_3$): ν : 3400 (NH), 2105 (N_2), 1625 (C=O), 1345 (SO_2), 1100 $C_{14}H_{19}N_3O_3S$ (309.38) : calcd. C 54.35, H 6.19, N 13.58, found: C 54.39, H 6.27, N 13.20.

Diazo-(*N*-tosyl-O-*tert*-butyldiphenylsilyl-L-serinyl)methane **16q**

Ts-Ser(OTBDPS)-OH **18q** (22.45 g, 45.11 mmol) was converted according to GP2 yielding 15.1 g (64%) of **16q** as a yellow waxy material, mp. 77-79 °C (dec). $[a]_D^{20}$ -33.0° (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz) δ : 1.01 (s, 9H, *t*Bu), 2.40 (s, 3H, $CH_3C_6H_4$), 3.48 (dd, part of AB, J_{AB} = 9.7 Hz, ^3J = 4.6 Hz, 1H, *CH*(H)OSi), 3.77 (m, 1H, *CH*NH), 3.91 (dd, part of AB, J_{AB} = 9.7 Hz, ^3J = 4.6 Hz, 1H, CH(*H*)OSi), 5.52 (d, ^3J = 7.0 Hz, 1H, N*H*), 5.69 (s, 1H, CHN_2), 7.18-7.68 (m, 14H, arom.). ^{13}C (100 MHz) δ : 19.2 ($C(CH_3)_3$), 21.5 ($CH_3C_6H_4$), 26.6 ($C(CH_3)_3$), 57.4 (CN_2), 63.8 (CH_2O), 127.0 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 129.8 ($C_{Ar}H$), 129.9 ($C_{Ar}H$), 132.1 (C_{Ar}), 132.4 (C_{Ar}), 135.4 ($C_{Ar}H$), 136.5 (C_{Ar}), 143.9 (C_{Ar}), 191.3 (*C*=O). IR ($CHCl_3$): ν : 3400 (NH), 2105 (N_2), 1630 (C=O), 1345 (SO_2), 1100. MS (CI) *m/z* (%) : 522(3) [M+1], 494(20) [M+1-N_2], 416(100).

Diazo-(*N*-tosyl-L-methionyl)methane **16r**

Ts-Met-OH **18r** (5.4 g, 17.8 mmol) was converted according to GP2 yielding 3.0 g (61%) of **16r** as a yellow solid, mp 101-102 °C [lit.[36] 101-102 °C], $[a]_D^{20}$ -42.2° (*c* = 1, $CHCl_3$) [lit.[36] $[a]_D^{20}$ -37.1° (*c* = 1, CH_2Cl_2)]. ^{1}H NMR (400 MHz) δ : 1.78 (m, 1H, CH_2CH_2S), 1.92 (m, 1H, CH_2CH_2S), 1.96 (s, 3H, SCH_3), 2.42 (s, 3H, $CH_3C_6H_4$), 2.45 (m, 2H, CH_2S) 3.96 (br s, 1H, *CH*NTs), 5.51 (s, 1H, CHN_2), 5.93 (d, ^3J = 8.2 Hz, N*H*), 7.30 (d, *J* = 8.3 Hz, 2H, $C_6H_4CH_3$), 7.73 (d, *J* = 8.3 Hz, 2H, $C_6H_4CH_3$). ^{13}C (100 MHz) δ : 15.2 (SCH_3), 21.4 ($CH_3C_6H_4$), 29.7 (CH_2S), 32.1 (CH_2CH_2S), 54.5 (CHN_2), 58.5 (CHNHTs), 127.1 ($C_{Ar}H$), 129.6 ($C_{Ar}H$), 136.6 (C_{Ar}), 143.8 (C_{Ar}), 192.2 (*C*=O). IR ($CHCl_3$): ν : 2110 (N_2), 1640 (C=O), 1365 (SO_2), 1100. MS (CI) *m/z* (%) : 328(24) [M+1], 300(100) [M+1-N_2].

Azetidin-3-ones 6

General procedure for the preparation of N-benzyloxycarbonyl protected azetidin-3-ones 6b and 6c (GP3)

Under an argon atmosphere the diazomethyl ketone was dissolved in dry CH_2Cl_2 (~0.2 M) and Et_3N (1 mol%) was added. After cooling in ice, $Rh_2(OAc)_4$ (0.5-1.0 mol%) was added and the green, bubbling solution was stirred over night during which the temperature was allowed to rise to ambient. The reaction mixture was concentrated *in vacuo* and the obtained azetidin-3-one purified by flash column chromatography (hexane/ethyl acetate 5:1 (v/v)).

(S)-2-*iso*Propyl-1-benzyloxycarbonyl-azetidin-3-one **6b**
Cbz-Val-CHN_2 **16b** (5.21 g, 18.9 mmol) was converted according to GP3 yielding 1.75 g (37%) of **6b** as a white crystalline material, after crystallisation (hexane/*iso*propyl ether 1 : 10 (v/v)), mp 43 °C [lit.[21a] 50-51 °C], $[a]_D^{20}$ +33.4 (*c* = 1, $CHCl_3$) [lit.[21a] +34.6° (*c* = 1, $CHCl_3$)]. ^1H NMR (100 MHz) δ : 1.03 (2xd, *J* = 6.8 Hz, 6H, $CH(CH_3)_2$), 2.24 (m, 1H, $CH(CH_3)_2$), 4.47 (dd, part of AB, J_{AB} = 17.4 Hz, *J* = 3.5 Hz, 1H, NC(*H*)HCO), 4.75 (d, part of AB, J_{AB} = 17.4 Hz, 1H, NC(*H*)HCO), 4.82 (m, 1H, C*H*iPr), 5.16 (s, 2H, CH_2Ph), 7.36 (s, 5H, C_6H_4). ^{13}C NMR (25 MHz, $CDCl_3$) δ : 17.4 (CH_3), 18.1 (CH_3), 29.9 ($C(CH_3)_2$), 67.6 (CH_2Ph), 69.7 (NCH_2), 88.7 (CH*i*Pr),128.1 ($C_{Ar}H$),128.3 ($C_{Ar}H$),128.5 ($C_{Ar}H$), 136.1 (C_{Ar}), 199.9 (C=O). IR ($CHCl_3$) ν : 1820 (C=O), 1720 (C=O, urethane). MS (CI) *m/z* (%) 247 (3) [M+1], 91 (100).

(S)-2-*tert*-Butyl-1-benzyloxycarbonyl-azetidin-3-one **6c**
Cbz-*t*Leu-CHN_2 **16c** (4.4 g, 15.2 mmol) was converted according to GP3 yielding 2.1 g (53%) of **6c** as a colourless oil, $[a]_D^{20}$ +2.1°(*c* = 1, $CHCl_3$). ^1H NMR (300 MHz) δ : 1.03 (s, 9H, *t*Bu), 4.48 (dd, part of AB, J_{AB} = 16.7 Hz, *J* = 4.0 Hz, 1H, NC(*H*)HCO), 4.70 (d, *J* = 4.0 Hz, 1H, C*H*tBu), 4.72 (d, *J* = 16.7 Hz, 1H, NC(*H*)HCO), 5.14 (s, 2H, CH_2Ph), 7.36 (m, 5H, C_6H_5). ^{13}C NMR (75 MHz) δ : 25.8 ($C(CH_3)_3$), 34.9 ($C(CH_3)_3$), 67.8 (CH_2Ph), 70.4 (NCH_2CO), 92.6 (CH*t*Bu), 128.2 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 136.2 (C_{Ar}), 200.2 (C=O). IR ($CHCl_3$) ν : 1820 (C=O), 1720 (C=O, urethane). MS (CI) *m/z* (%) : 218 (17), 142 (12), 98 (25), 91 (100).

(S)-2-Methyl-1-trityl-azetidin-3-on **6d**
A solution of Trt-Ala-CHN_2 **16d** (706 mg, 1.99 mmol) in 25 ml dry diethyl ether was added drop wise to a solution of 4 drops of concentrated sulfuric acid in 20 ml of dry diethyl ether. An slow evolution of gas was observed and the mixture was stirred until TLC-analysis showed completion of the reaction (approx. 3 h). The reaction was quenched by the addition of 20 ml of a saturated aqueous $NaHCO_3$-solution. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate 5:1 (v/v)) followed by crystallisation from di*iso*propyl ether gave 500 mg (77%) **6d** as white crystals, mp 166-168 °C, $[a]_D^{20}$ -3.76 ° (*c* = 1, $CHCl_3$), ^1H NMR (100 MHz) δ : 1.31 (d, ^3J = 6.7 Hz, 3H, CH_3), 3.63 (dd, part of AB, J_{AB} = 15.9 Hz, *J* = 1.3 Hz, 1H, NC(*H*)HCO), 3.76 (m, 1H, $CHCH_3$), 4.27 (dd, part of AB, J_{AB} = 15.9 Hz, *J* = 4.5 Hz, 1H, NC(*H*)HCO), 7.07-7.62 (m, 15H, $C(C_6H_5)_3$). ^{13}C NMR (25 MHz) δ : 16. 6 (CH_3), 67.6 (NCH_2CO), 75.4 ($CHCH_3$), 75.7 ($C(C_6H_5)_3$), 126.7 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 129.3 ($C_{Ar}H$), 142.2 (C_{Ar}), 204.8 (C=O). IR ($CHCl_3$) ν :

1815 (C=O). MS (CI) *m/z* (%) : 328 (12) [M+1], 243(100). $C_{23}H_{21}NO$ (327.42) calcd. C 84.37, H 6.64, N 4.28 found: C 84.11 H 6.47 N 4.40.

General procedure for the preparation of N-tosyl azetidin-3-ones 6i-6q (GP4)

To a solution of the diazomethyl ketone in dry CH_2Cl_2 (~ 0.01.M) a solution of $BF_3{\cdot}OEt_2$ (1 mol%) was carefully added drop wise. An instantaneous evolution of nitrogen gas was observed and the reaction mixture was stirred at ambient temperature until the effervescence ceased. The reaction was quenched by the addition of a saturated aqueous $NaHCO_3$ solution, after which the organic layer was washed with water and brine, dried with $MgSO_4$ and concentrated *in vacuo*. The azetidin-3-ones thus obtained are essentially pure solids, which can be crystallised from hexane.

(S)-2-Methyl-1-tosyl-azetidin-3-one **6i**

Ts-Ala-CHN_2 **16i** (133 mg, 0.5 mmol) was converted according to GP4 yielding 104 mg (88%) of **6i** as a white solid, mp 80 °C [lit.[36] 76-77 °C, lit.[53] 78-79 °C], $[a]_D^{20}$ +67.2 ° (*c* = 1, $CHCl_3$) [lit.[36] $[a]_D^{20}$ +55 ° (*c* = 1, $CHCl_3$), lit.[53] $[a]_D^{20}$ +80 ° (*c* = 1, $CHCl_3$)]. ^{1}H NMR (100 MHz) δ : 1.45 (d, ^3J = 6.9 Hz, 3H, CH_3), 2.47 (s, 3H, $CH_3C_6H_4$), 4.50 (d, *J* = 2.1 Hz, 2H, NCH_2CO), 4.76 (m, 1H, $CHCH_3$), 7.39 (d, *J* = 8.2 Hz, 2H, $C_6H_4CH_3$), 7.72 (d, *J* = 8.2 Hz, 2H, $C_6H_4CH_3$). ^{13}C NMR (25 MHz) δ : 15.7 (CH_3), 21.6 ($CH_3C_6H_4$), 69.9 (NCH_2CO), 81.0 ($CHCH_3$), 128.4 ($C_{Ar}H$), 130.1 ($C_{Ar}H$), 131.6 (C_{Ar}), 145.0 (C_{Ar}), 196.7 (C=O). IR ($CHCl_3$) ν : 1820 (C=O), 1350 (SO_2), 1150. MS *m/z* (%) : 240 (4) [M^+ + 1], 155 (2) [Ts], 91 (15), 56 (100) [M^+ - Ts - CO].

(S)-2-Benzyl-1-tosyl-azetidin-3-one **6j**

16j 343 mg (1 mmol) was converted according to GP4 yielding 300 mg (95%) of **6j** as a white solid, mp 115-116 °C [lit.[36] 97-98 °C], $[a]_D^{20}$ +106.8° (*c* =1, $CHCl_3$) [lit.[36] $[a]_D^{20}$ +4.7° (*c* =1, $CHCl_3$)]. ^{1}H NMR (100 MHz) δ : 2.46 (s, 3H, $CH_3C_6H_4$), 3.13 (d, ^3J = 5.6 Hz, 2H, CH_2Ph), 4.14 (dd, part of AB, J_{AB} = 16.1 Hz, J = 3.7 Hz, 1H, NC(*H*)HCO), 4.43 (d, part of AB, J_{AB} = 16.1 Hz, 1H, NC(*H*)HCO), 4.95 (m, 1H, C*H*Bn), 7.25 (m, 5H, C_6H_5), 7.37 (d, *J* = 8.1 Hz, 2H, $C_6H_4CH_3$), 7.76 (d, *J* = 8.1 Hz, 2H, $C_6H_4CH_3$). ^{13}C NMR (25 MHz) δ : 21.6 ($CH_3C_6H_4$), 36.6 (CH_2Ph), 69.9 (NCH_2CO), 85.3 (CHBn), 127.1 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 130.0 ($C_{Ar}H$), 130.1 ($C_{Ar}H$), 131.6 (C_{ar}), 135.0 (C_{ar}), 145.0 (C_{ar}), 196.0 (C=O). IR ($CHCl_3$) ν : 1825 (C=O), 1600, 1360, 1160. MS (CI) *m/z* (%) : 316 (7) [M^+ + 1], 155 (6) [Ts], 132 (100) [M^+ - Ts - CO], 91 (11).

(S)-2-*iso*Propyl-1-tosyl-azetidin-3-one **6k**

16k 298 mg (1 mmol) was converted according to GP4 yielding 266g (99%) of **6k** as a white solid, mp 95 °C, $[a]_D^{20}$ +51.1° (*c* = 1, $CHCl_3$), ^{1}H NMR (400 MHz) δ : 1.05 (dd, ^3J = 6.6 Hz, 6H, $CH(CH_3)_2$), 2.13 (m, 1H, $CH(CH_3)_2$), 2.47 (s, 3H, $CH_3C_6H_4$), 4.41 (dd, part of AB, J_{AB} = 16.4 Hz, *J* = 3.8 Hz, 1H, NC(*H*)HCO), 4.50 (d, part of AB, J_{AB} = 16.4 Hz, 1H, NC(*H*)HCO), 4.62 (m, 1H, C*H*i*Pr*), 7.39 (d, *J* = 8.1 Hz, 2H, $C_6H_4CH_3$), 7.78 (d, *J* = 8.1 Hz, 2H, $C_6H_4CH_3$). ^{13}C NMR (25 MHz) δ : 17.5 and 18.2 ($CH(CH_3)_2$, 21.8 ($CH_3C_6H_4$), 30.5 ($CH(CH_3)_2$, 70.4 (NCH_2CO), 90.4 (CH*i*Pr), 128.5 ($C_{Ar}H$), 130.1 ($C_{Ar}H$), 132.0 (C_{Ar}), 145.0 (C_{Ar}), 197.3 (C=O). IR ($CHCl_3$) ν 1810 (C=O), 1595, 1340, 1150, 1100. MS (EI) *m/z* (%): 267 (2) [M^+], 240 (94) [M^+-CO], 155 (50)

[$C_7H_7SO_2^+$], 91 (100) [$C_7H_7^+$]. $C_{13}H_{17}NO_3S$ (267.34): calcd. C 58.41, H 6.41, N 5.24 found: C 58.52, H 6.15, N 5.09

(S)-2-*iso*Butyl-1-tosyl-azetidin-3-one **6m**

16m 308 mg (1 mmol) was converted according to GP4 yielding 267 mg (95 %) of **6m** as a white solid, mp 62 °C, $[a]_D^{20}$ +65.8° (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz) δ : 0.92 (dd, ^3J = 6.6 Hz, 6H, CH(CH_3)$_2$), 1.74 (m, 2H, CH_2*i*Pr), 1.91 (m, 1H, $CH(CH_3)_2$), 2.47 (s, 3H, $CH_3C_6H_4$), 4.46 (d, part of AB, J_{AB} = 16.2 Hz, 1H, NC(*H*)HCO), 4.51 (d, part of AB, J_{AB} = 16.2 Hz, 1H, NC(*H*)HCO), 4.75 (m, 1H, C*H*i*Bu*), 7.40 (d, *J* = 8.1 Hz, 2H, $C_6H_4CH_3$), 7.78 (d, *J* = 8.1 Hz, 2H, $C_6H_4CH_3$). ^{13}C NMR (100 MHz) δ : 21.6 ($CH_3C_6H_4$), 22.4 and 22.6 ($CH(CH_3)_2$), 24.4($CH(CH_3)_2$), 39.7 (CH_2*i*Pr), 69.7 (NCH_2CO), 83.9 (C*H*i*Bu*), 128.4 ($C_{Ar}H$), 130.0 ($C_{Ar}H$), 131.6 (C_{Ar}), 144.9 (C_{Ar}), 197.2 (*C*=O). IR ($CHCl_3$) ν : 1815 (C=O), 1595, 1350, 1150, 1100. MS *m/z* (%): 281 (6) [M^+], 155 (2) [$C_7H_7SO_2^+$], 91 (12) [$C_7H_7^+$], 57 (19) [$C_4H_9^+$], 40 (100).
$C_{14}H_{19}NO_3S$ (281.36): calcd. C 59.76, H 6.81 N 4.98 found: C 59.87, H 6.45, N 5.09

(S)-2-*sec*-Butyl-1-tosyl-azetidin-3-one **6n**

16n 309 mg (1 mmol) was converted according to GP4 yielding 264 mg (94%) of **6n** as a white solid, mp 89 °C, $[a]_D^{20}$ +74.5° (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz) δ : 0.92 (t, ^3J = 7.4 Hz, 3H, CH_3CH_2), 1.04 (d, ^3J = 6.9 Hz, 3H, CH_3CH), 1.35 (m, 1H, C(*H*)HCH_3), 1.52 (m, 1H, C(*H*)HCH_3), 1.90 (m, 1H, C*H*(Me)Et), 2.47 (s, 3H, $CH_3C_6H_4$), 4.40 (dd, part of AB, J_{AB} = 16.3 Hz, *J* = 3.6 Hz, 1H, NC(*H*)HCO), 4.47 (d, part of AB, J_{AB} = 16.3 Hz, 1H, NC(*H*)HCO), 4.67 (dd, ^3J = 5.0 Hz, *J* = 3.7 Hz, 1H, C*H*s*Bu*), 7.39 (d, *J* = 8.2 Hz, 2H, $C_6H_4CH_3$), 7.77 (d, *J* = 8.2 Hz, 2H, $C_6H_4CH_3$). ^{13}C NMR (100 MHz) δ : 11.4 (CH_3CH_2), 14.2 (CH_3CH), 21.6 ($CH_3C_6H_4$), 25.3 (CH_2CH_3), 37.0 (CH(Me)Et), 70.0 (NCH_2CO), 89.4 (C*H*s*Bu*), 128.3 ($C_{Ar}H$), 130.0 ($C_{Ar}H$), 131.8 (C_{Ar}), 144.9 (C_{Ar}), 197.1 (*C*=O). IR ($CHCl_3$) ν : 1820 (C=O), 1600, 1355, 1150, 1100. MS *m/z* (%): 281 (6) [M^+], 91 (10) [$C_7H_7^+$], 57 (16) [$C_4H_9^+$], 40 (100). $C_{14}H_{19}NO_3S$ (281.36): calcd. C 59.76, H 6.81 N 4.98 found: C 59.86, H 6.52, N 5.06

(S)-2-*tert*-Butyl-1-tosyl-azetidin-3-one **6p**

16p 941 mg (3 mmol) was converted according to GP4 yielding 830 mg (97 %) of **6p** as a white solid, mp 123 °C, $[a]_D^{20}$ +21.9 ° (*c* = 1, $CHCl_3$). ^1H NMR (100 MHz) δ : 1.05 (s, 9H, *t*Bu), 2.46 (s, 3H, $CH_3C_6H_4$), 4.38 (dd, part of AB, J_{AB} = 16.6 Hz, *J* = 3.0 Hz, 1H, NC(*H*)HCO), 4.51 (d, *J* = 3.0 Hz, 1H, C*H*t*Bu*), 4.60 (d, part of AB, J_{AB} = 16.6 Hz, 1H, NC(*H*)HCO), 7.38 (d, *J* = 8.2 Hz, 2H, $C_6H_4CH_3$), 7.78 (d, *J* = 8.2 Hz, 2H, $C_6H_4CH_3$). ^{13}C NMR (25 MHz) δ : 21.5 ($CH_3C_6H_4$), 25.7 ($C(CH_3)_3$), 34.7 ($C(CH_3)_3$), 71.0 (NCH_2CO), 93.9 (C*H*t*Bu*), 128.3 ($C_{Ar}H$), 130.0 ($C_{Ar}H$), 132.6 (C_{Ar}), 144.7 (C_{Ar}), 197.7 (*C*=O). IR ($CHCl_3$) ν (cm^{-1}) : 1815 (C=O), 1600, 1355, 1160. MS (CI) *m/z* (%) : 282 (12) [M^+ + 1], 155 (10) [Ts], 98 (100) [M^+ - Ts - CO]. $C_{14}H_{19}NO_3S$ (281.36): calcd. C 59.76 H 6.81 N 4.98 found: C 59.29 H 7.01 N 5.00.

(S)-2-*tert*-Butyldiphenylsilyl-hydroxymethyl-1-tosyl-azetidin-3-one **6q**

16q Ts-Ser(OTBDPS)-CHN_2 (107 mg, 0.21 mmol) was converted according to GP4 yielding 100 mg (96%) of **6q** as white crystals, mp 128-129 °C, $[a]_D^{20}$ +58.8 ° (c = 1, $CHCl_3$). ^1H NMR (100 MHz) δ : 1.02 (s, 9H, *t*Bu), 2.45 (s, 3H, $CH_3C_6H_4$), 3.92 (d, ^3J = 2.5 Hz, 2H, NCH_2CO), 4.59 (d, ^3J = 1.9 Hz, 2H, $CH_2OTBDPS$), 4.87 (m, 1H, $CHCH_2OTBDPS$), 7.25-7.80 (m, 14H, 2x C_6H_5 and C_6H_4). ^{13}C NMR (25 MHz) δ : 19.3 ($C(CH_3)_3$), 21.8 ($CH_3C_6H_4$), 26.7 ($C(CH_3)_3$), 61.9 ($CH_2OTBDPS$), 71.0 (NCH_2CO), 88.5 ($CHCH_2OTBDPS$), 127.9 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 130.0 ($C_{Ar}H$), 130.1 ($C_{Ar}H$), 132.6 (C_{Ar}), 132.7 (C_{Ar}), 132.8 (C_{Ar}), 135.6 ($C_{Ar}H$), 135.7 ($C_{Ar}H$), 144.7 (C_{Ar}), 195.0 (C=O). IR ($CHCl_3$) ν : 1820 (C=O), 1590, 1350 (SO_2). $C_{27}H_{31}NO_4SiS$ (493.69) calc. C 65.69 H 6.33 N 2.84 found C 65.43 H 6.16 N 2.96.

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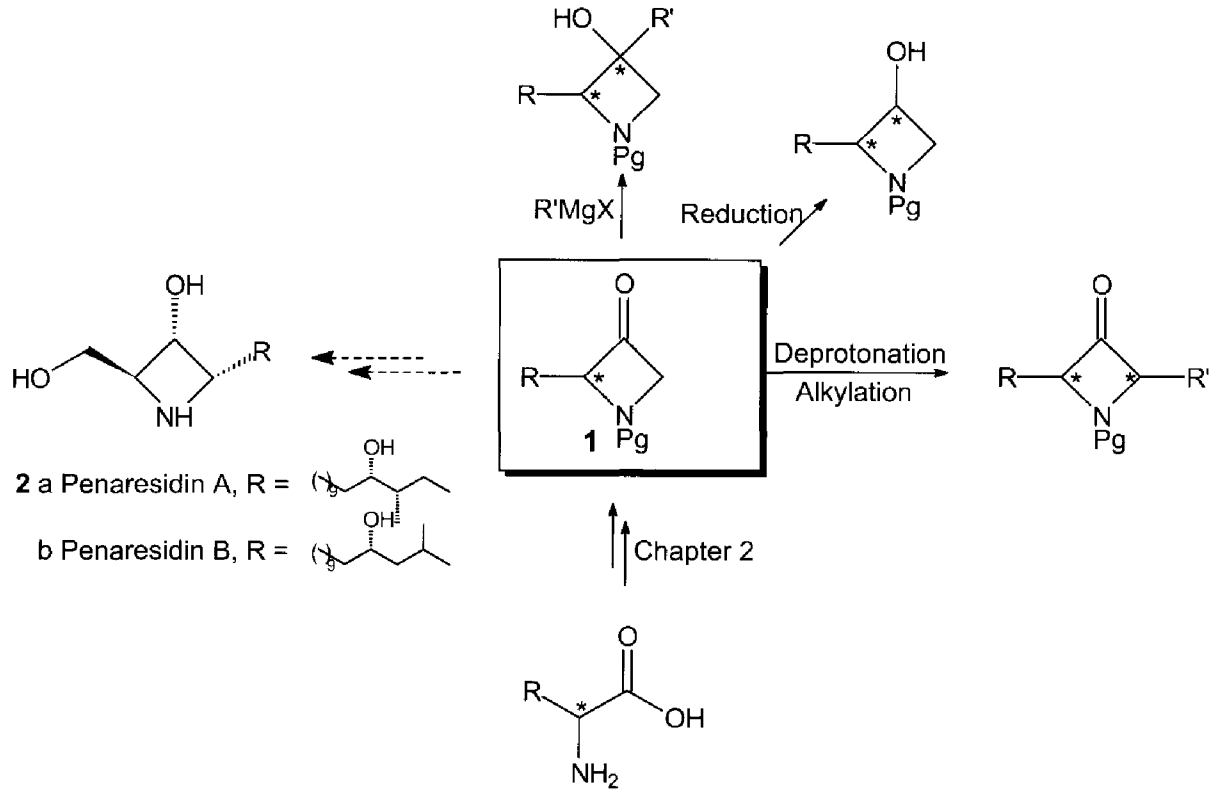
3 Diastereoselective transformations of 2-substituted azetidin-3-ones

3.1 Introduction

Functionalised azetidines occur in nature, in spite of the fact that these small-ring heterocycles are considerably strained and show an inherent high propensity to ring-opening reactions. Examples have been given in Chapter 2 (section 2.1). Several of these heterocycles posses interesting biological and pharmacological activity and have therefore received considerable attention[1]. However, the synthetic accessibility of these four-membered ring nitrogen heterocycles in general is hampered by the fact that the synthetic arsenal for enantiomerically pure azetidines is rather limited. The long and often complex synthetic routes that were followed to obtain some of these, even simple, naturally occurring azetidines are an illustration thereof[2]. As shown in the preceding chapter enantiopure 2-substituted azetidin-3-ones can readily be prepared from α-amino acids *via* an intramolecular cyclisation reaction of the corresponding amino diazomethyl ketones. These azetidines can serve as potential substrates for the preparation of a variety of substituted azetidines by performing diastereoselective transformations. The results of these studies are described in this chapter.

From biological and pharmacological point of view 3-hydroxylated azetidines are of particular interest[3]. For that reason the emphasis was on transformations that might result in an improved accessibility of this particular class of compounds. For this purpose the *reduction* of and *Grignard reactions* with azetidin-3-ones were considered. Since many naturally occurring azetidines are tri-substituted, *e.g.* the Penaresidines **2**, also the functionalisation at C4 by *deprotonation* and subsequent *alkylation* of azetidin-3-ones was investigated. The planned molecular transformations of azetidin-3-ones are depicted in scheme 1.

Scheme 1 *Transformations of 2-substituted azetidin-3-ones*



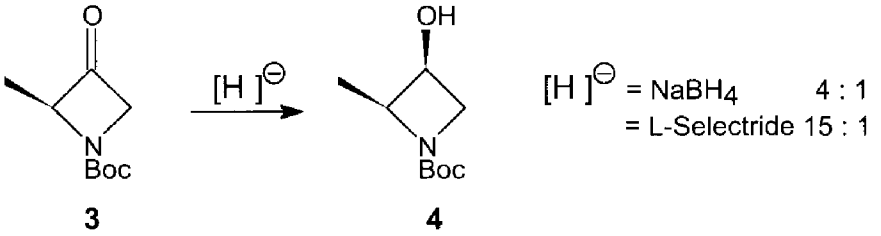
3.2 Reduction of 2-substituted azetidin-3-ones

The diastereoselective reduction of α-substituted cycloketones has been studied extensively and has been reviewed comprehensively[4]. This research has resulted in the development of several reductive methodologies for the preparation of cyclic secondary alcohols with excellent (>99 %) diastereoselectivity. Depending on the reducing agent used, the stereochemical outcome of these reductions, can be explained in terms of either *steric approach control* or *product development control*[5]. Product development control, which is based on the relative thermodynamic stability of the conceivable products, plays a role especially in the case of small reducing agents, *e.g.* lithium aluminium hydride, although also stereoelectronic effects have to be taken into consideration[6]. Steric approach control, based on the competitive attacks from a favored (unhindered) or an unfavored (hindered) side, is a determining factor in the case of sterically demanding hydride donors, *e.g.* L-Selectride® (lithium tri-*sec*-butylborohydride). With L-Selectride and related, bulky borohydrides, excellent results are often obtained.

Most frequently, five- and six-membered ring ketones, *e.g.* cyclopentanones, cyclohexanones and piperidones, have been used as substrate. In contrast, four-membered ring ketones received little attention. The limited information that *is* available on the reduction of azetidin-3-ones however, seems to indicate that similar

stereoselectivities can be obtained as observed for five- and six-membered cycloketones (scheme 2)[7].

Scheme 2 *Diastereoselective reduction of (S) 2-methyl-1-tert-butyloxycarbonyl-azetidin-3-one* **3**[7]

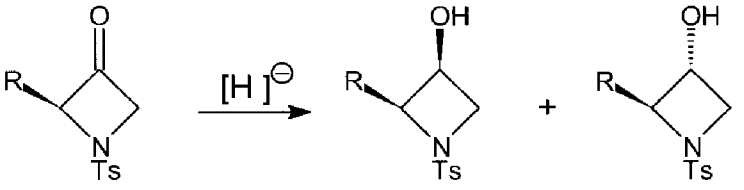


3 **4**

The relatively small hydride donor $NaBH_4$ gave a poor selectivity, whereas with L-Selectride® the *anti* alcohol was obtained with an excellent stereoselectivity, despite the fact that the directing stereogenic centre only carries a small methyl-substituent. This literature report[7] is encouraging for the use of azetidin-3-ones as synthon for the synthesis of enantiopure 3-hydroxy azetidines. To extend the scope the diastereoselectivity of the reduction of azetidin-3-ones was investigated with several reducing agents and substrates with substituents of increasing size.

The results of this comparative study are collected in table 1.

Table 1 *Diastereoselectivities in the reduction of azetidin-3-ones*



5-7 **8-10a** *syn* **8-10b** *anti*

azetidin-3-one	R	product	reagent	product ratio *syn/anti*
5	Me	**8**	$LiAlH_4$	1:4
6	*i*Pr	**9**	$LiAlH_4$	2:1
7	*t*Bu	**10**	$LiAlH_4$	15:1
5	Me	**8**	L-Selectride	1:3
6	*i*Pr	**9**	L-Selectride	1:1.2
7	*t*Bu	**10**	L-Selectride	>99:1

In most cases, the secondary alcohols were obtained as a mixture of inseparable diastereoisomers, which made interpretation of the NMR spectra rather difficult. However, spectra run at elevated temperature (40-50°C) resulted in considerable improvement of the resolution, giving near base line separation of the individual signals. In combination with 2D-COSY NMR spectroscopy this was sufficient for unambiguous interpretation of the spectra. Determination of the obtained selectivities, was carried out by integration of the NMR signals and was independently confirmed by GC-analysis of the corresponding acetates.

The configuration of the newly formed chiral centre at C-3 in both the major and minor isomer, was assigned by NMR spectroscopy, on the basis of the assumption that $^3J_{2,3}$ in the *syn*-isomer is larger than in the corresponding *anti*-isomer (6-8 Hz *vs.* 4-5 Hz). A similar assumption has been used previously for the assignment of configuration of other 3-hydroxy azetidines[9]. Conversion of the alcohol, derived from **5** by reduction with lithium aluminium hydride, into the corresponding 3,5-dinitrobenzoate, enabled separation and hence individual NMR-analysis of the two diastereoisomers. The major product displayed the largest coupling between H-2 and H-3, suggesting the *syn*-configuration. This was unambiguously confirmed by X-Ray analysis of this product (Figure 1).

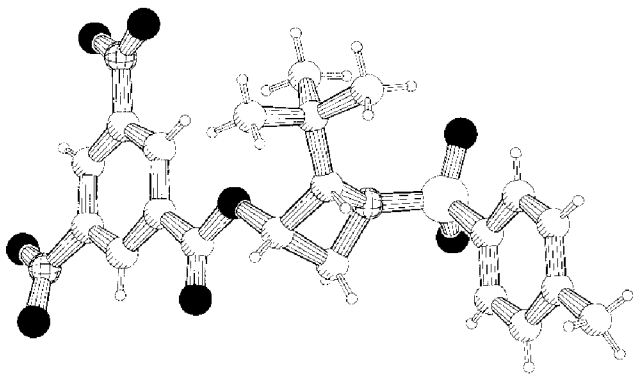


Figure 1 PLUTON drawing of the X-ray crystal structure of the 3,5-dinitrobenzoate ester **10a'**

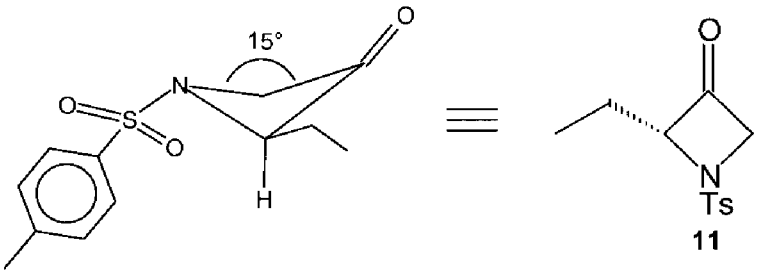
Comparison of the results obtained with azetidin-3-one **5** with those reported[7] for the close analogue **3** (Scheme 2), reveals some striking differences. Whilst the diastereoselectivity of the lithium aluminium hydride reduction of **5** matches that of the sodium borohydride reduction of **3**, the excellent asymmetric induction of the L-Selectride reduction of the latter, was not observed for **5**. The use of other bulky reducing agents, *e.g.* DIBALH or chiral oxazaborolidines, did not change this. Furthermore, in contrast to the result reported for azetidinone **3**, in all cases the

thermodynamically most stable *anti*-alcohol was obtained as the major product from the reduction of **5**.

Further analysis of the results reveals that the diastereoselectivity of the reduction is reversed with increasing size of the α-substituent. Going from the relatively small methyl group to the bulky *tert*-butyl group, improves the initially poor *anti*-selectivity to (almost) complete *syn*-selectivity, both with lithium aluminium hydride and L-Selectride.

In order to rationalise the observed diastereoselectivities during the various reductions of azetidin-3-ones, it is essential to have information about the three-dimensional structure of these substrates. Crystallographic data for the *N*-tosyl 2-ethyl-azetidin-3-one **11**[9] shows that the rigid four-membered ring is not planar, the infliction along the C2-C3-axis being 15° (Figure 2). Both the pyramidal nitrogen atom and the oxygen atom of the carbonyl function, are tilted out of the plane defined by the three carbon atoms and the two substituents are disposed in pseudoequatorial positions.

Figure 2 *3D-representation of the crystal structure of N-tosyl 2-ethyl-azetidin-3-one*



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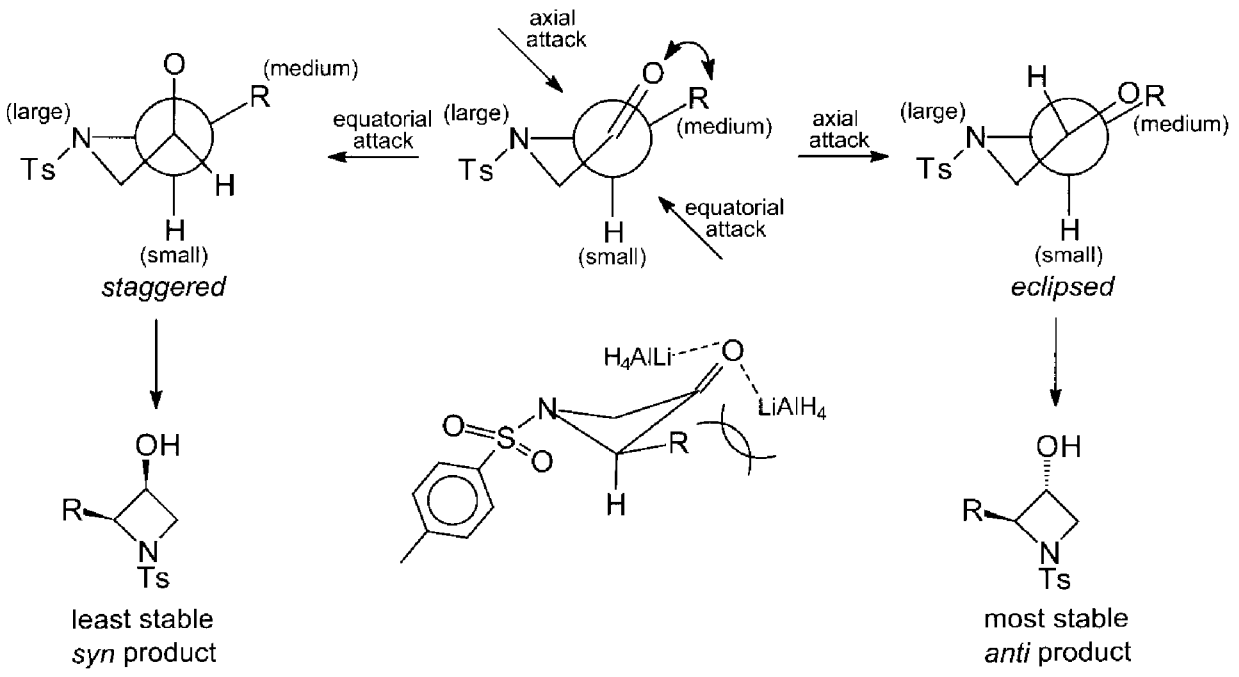
As indicated earlier, the stereochemical outcome of reduction of cyclic ketones is determined by two fundamentally different factors : *product development control* and *steric approach control*. In the case of small, sterically undemanding reducing agents like lithium aluminium hydride, the stereochemistry is primarily governed by product control, whereby the product ratio is determined by the relative thermodynamic stability of the possible products. This means that the more stable *anti* alcohol is obtained as the major product, as was observed for the reduction of azetidin-3-one **5** with lithium aluminium hydride. In addition, stereoelectronic effects have been used to explain the observed (axial) π-face selectivity in the reduction of cycloketones. Cieplack *et al.* reasoned that the antiperiplanar axial C-H bonds can preferentially stabilise the transition state for axial attack by electron donation into the anti-bonding orbital of the developing bond to the nucleophile[10]. In this theory, it is assumed that C-H bonds are better hyperconjugative electron donors than C-C bonds, a view that is still under debate[11]. Alternative models[12] explain the axial attack by hyperconjugative stabilisation of the incipient σ-bond by the best

antiperiplanar electron *acceptor*, again being the axial C-H bond. The disconcerting aspect of Cieplack's theory however, does not prevent its application to the reduction of the azetidin-3-ones **5-7**. In this case, the equatorial transition state is not to be stabilised by C-C bonds, but by electron poor C-NTs bonds, which may be regarded as a poorer electron donor than the axial C-H bond, thus favouring the formation of the *anti* alcohol. However, both aforementioned factors are counterbalanced by torsional effects. As can be seen in the Felkin-Ahn[12a,b,13] representation of the azetidin-3-one (Figure 3), the carbonyl is almost eclipsed with the pseudoequatorial C-2 substituent. This torsional strain increases by an axial attack, as the oxygen atom moves through an unfavourable fully eclipsed arrangement, but is relieved by an equatorial attack, in which the oxygen atom moves away from the plane of the substituent, resulting in a favourable staggered arrangement. Increasing the size of the substituent will make the eclipsed conformation, and therefore the axial attack, less attractive, counterbalancing the product development and stereoelectronic control, thus promoting the formation of the less stable *syn* alcohol.

Figure 3 *Factors influencing the stereochemical outcome of $LiAlH_4$ reduction of azetidin-3-ones*



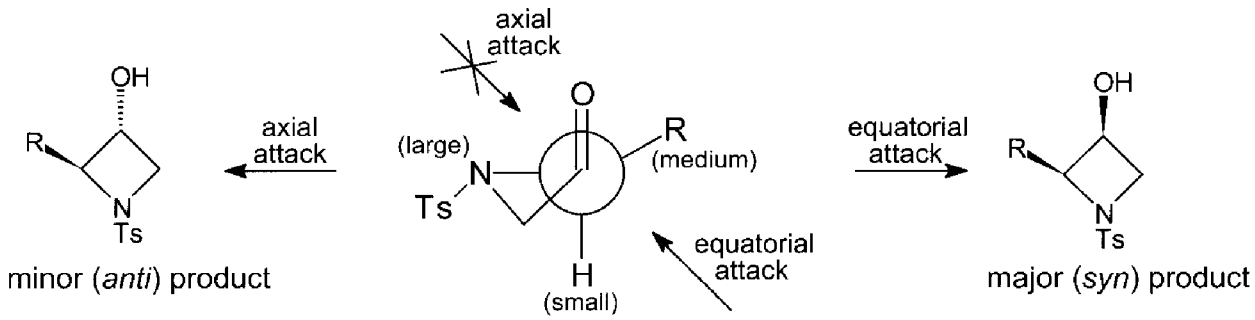
The stereochemical outcome of the reaction is further influenced by the fact that reductions with lithium aluminium hydride involve association of the carbonyl oxygen with Li^+ during the hydride transfer [5]. For a relatively small α-substituent, this complexation does not play an important role, as it can equally well take place at either face of the molecule. However, increasing the size of the substituent makes, due to unfavourable steric interaction (steric approach control, *vide infra*),

complexation at the equatorial face of the molecule more difficult. Hence, the reducing agent will preferably co-ordinate at the axial face of the molecule, thereby shielding this diastereotopic face of the ketone, which results in a preferred hydride transfer from the opposite unshielded equatorial side, leading to the *syn*-product (Figure 3). The rather high stereoselectivity of the reduction of hydroxy- and amino ketones, including *N*-alkyl substituted azetidin-3-ones[18], has been attributed to similar factors. It is assumed that the axial face is shielded due to coordination of the reducing agent between the carbonyl oxygen and the electron rich amine function. For azetidine-3-ones **5-7**, the amino function is electron poor and therefore similar coordination seems unlikely. The net effect however, is the same, *viz.* shielding of the axial face and preferred equatorial hydride transfer, leading to the *syn*-product.

In summary, during the reduction with lithium aluminium hydride four factors that control the facial selectivity have to be taken into account, *viz.* product development control, stereoelectronic factors, torsional strain and complexation by the reducing agent. The first two factors promote *anti* selectivity, whereas the other two lead to *syn* selectivity. The actual outcome of the stereocontrol is determined by a delicate balance between these factors. For substrate **5** lithium aluminium hydride reduction leads predominantly to the *anti*-product, suggesting that the first two factors are most important. With increasing size of the α-substituent the last mentioned two effects seem to prevail. For substrate **6** (R=*i*Pr) there is some preference for the *syn*-product, while for substrate **7** (R=*t*Bu) there is a clear *syn* selectivity.

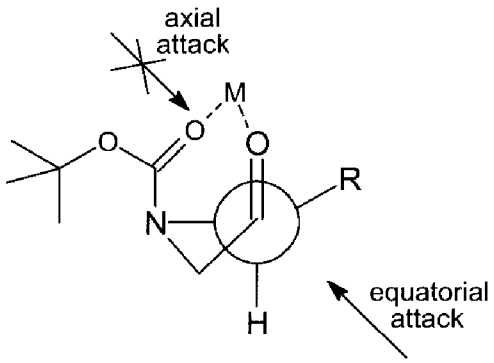
For bulky reducing reagents the stereocontrol is fully governed by steric factors. Steric approach control implies an early, reactant-like, transition state in which the entering nucleophile approaches the least hindered face of the ketone. This concept, is best explained using a Felkin-Ahn model of the azetidin-3-ones. In this representation, which is a modification of the Cram model[14], the largest substituent is placed perpendicular to the carbonyl group. To value the role of electronic factors in stabilising the transition state, electron-withdrawing groups are regarded as the largest substituent, independent of their steric bulk. As a result, the Felkin-Ahn model of azetidinones **5-7** is as depicted in Figure 4. The perpendicular orientation of the largest substituent, allows the bulky nucleophile to approach the carbonyl group *anti* with respect to this group, thus most effectively avoiding van der Waals repulsion with the large and medium sized substituents. This preferential equatorial attack, is not strictly *anti*, but the nucleophile rather follows the so-called Bürgi Dunitz trajectory[15], approaching the carbonyl group under an angle of 109°. In this way, destabilising interactions arising from out-of-phase overlap with the oxygen atom and four-electron interaction with the HOMO of the substrate, are reduced.

Figure 4 *Steric approach control in the reduction of 2-substituted azetidin-3-ones*



Following this concept of steric approach control, the reduction of azetidin-3-one **7**, leads to the exclusive formation of the thermodynamically less stable *syn* alcohol **10a**. The same holds for the reduction of azetidinone **3** by this reducing agent, the lower selectivity is due to the sterically less demanding methyl substituent (Scheme 2).
The selectivity for the selectride reduction of azetidin-3-ones **5** and **6** indicate that other factors than steric ones must play a role. For **5** the *anti*-product predominates, while for **6** a meagre preference for the *syn*-product was found. Probably, stereoelectronic factors come into play which counterbalance the steric approach control. For substrate **6** the steric approach control and the stereoelectronic effect equal out to a large extent. Nevertheless, this observation is remarkable, usually steric effects in selectride reductions show a clear cut predominance. The difference in behaviour of the substrates **3** and **5** deserves attention. The only structural difference is their substituent at nitrogen. The *tert*-butyloxycarbonyl group has a positive effect on the selectivity which suggests an extra chelation effect of the reducing agent with this group in a manner as depicted in Figure 5.

Figure 5 *Syn-selectivity due to chelation in azetidin-3-one* **3**



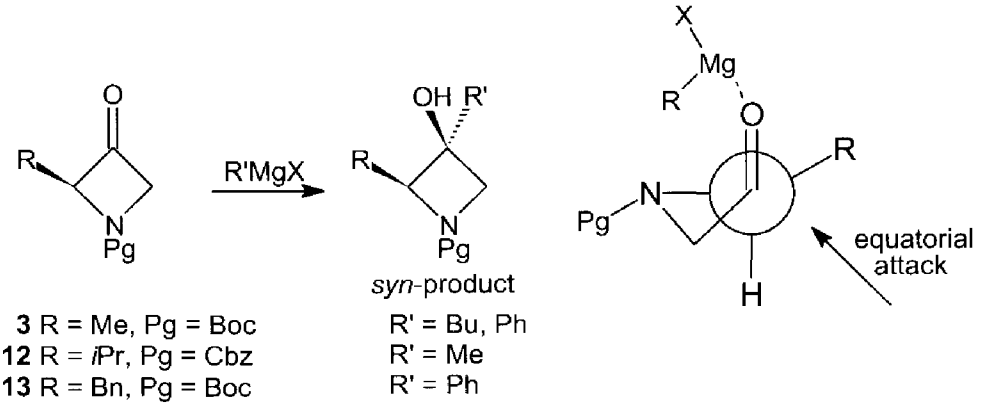
The axial face undergoes an effective shielding, which results in a preferential equatorial approach in the hydride transfer. A similar coordination is apparently much less effective for the N-tosyl group, resulting in an almost equal amount of *syn*- and *anti*-product.

In summary, the results obtained for the reduction of N-tosyl 2-substituted azetidin-3-ones show that for the very bulky *tert*-butyl substituent a high selectivity is achieved. For the methyl and *iso*propyl substituted four-membered rings the selectivity is unusually low. As a consequence, these N-tosyl substituted azetidin-3-ones in general are not as ideal as chiral synthons as was predicted. The mixtures of diastereomeric secondary alcohols are difficult to separate, which restricts their practical use.

3.3 Grignard reaction with 2-substituted azetidin-3-ones

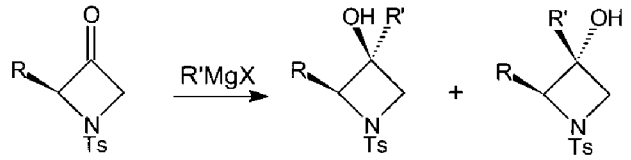
The reaction of ketones with organometallics is one of the most efficient ways for the preparation of tertiary alcohols. Especially organomagnesium compounds have been used extensively. Application of these Grignard reagents to α-substituted cycloketones, *e.g.* 2-alkyl cyclopentanones and 2-alkyl cyclohexanones, give in a steric approach controlled reaction, the axial alcohols with moderate to excellent diastereoselectivity[16]. Most interestingly, the reaction of 2-substituted azetidin-3-ones with several Grignard reagents is reported to proceed with complete stereoselectivity, to give the *syn*-alcohols as the exclusive product[7] (Scheme 3).

Scheme 3 *Stereoselective Grignard reaction of some 2-substituted azetidin-3-ones*



The completely selective equatorial attack of the Grignard reagents can be explained by invoking steric approach control. As is usually the case in Grignard reactions, the organometallic reagent serves as Lewis acid by coordinating with the carbonyl group. Subsequent attack of the Grignard reagent will now occur from the non-shielded equatorial face (*cf.* Scheme 3) to give the product in which the alcohol group is positioned *syn* with respect to the 2-substituent in the four-membered ring heterocycle. In the azetidin-3-ones investigated so far (Scheme 3) no example of an *N*-tosyl substrate was present. Therefore, such compounds were subjected to a reaction with several Grignard reagents. The results are collected in Table 2.

Table 2 *Diastereoselectivity of Grignard reactions with N-tosyl azetidin-3-ones*



syn **16-31a** *anti* **16-31b**

azetidinone	R	R′	*syn* : *anti*	yield (%)
5	CH_3	CH_3	50 : 50	73
5	CH_3	$CH{=}CH_2$	100 : 0	95
5	CH_3	$CH_2CH{=}CH_2$	67 : 33	71
5	CH_3	C_6H_5	100 : 0	25
14	CH_2Ph	CH_3	100 : 0	73
14	CH_2Ph	$CH{=}CH_2$	100 : 0	94
14	CH_2Ph	$CH_2CH{=}CH_2$	67 : 33	91
14	CH_2Ph	C_6H_5	100 : 0	80
6	$CH(CH_3)_3$	CH_3	100 : 0	81
6	$CH(CH_3)_3$	$CH{=}CH_2$	100 : 0	96
6	$CH(CH_3)_3$	$CH_2CH{=}CH_2$	100 : 0	90
6	$CH(CH_3)_3$	C_6H_5	100 : 0	91
15	$CH_2OSTBDP$	CH_3	100 : 0	95
15	$CH_2OSTBDP$	$CH{=}CH_2$	100 : 0	83
15	$CH_2OSTBDP$	$CH_2CH{=}CH_2$	100 : 0	80
15	$CH_2OSTBDP$	C_6H_5	100 : 0	97

In practically all cases the addition of Grignard reagents led to the formation of tertiary alcohols as a single diastereomer. Their *syn* configuration, was established by an X-Ray crystal structure analysis of product **26a** (figure 6).

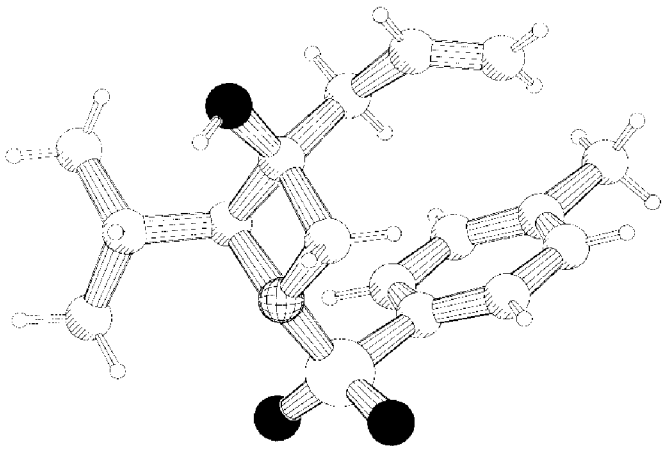


Figure 6 PLUTON drawing of the X-ray crystal structure of azetidin-3-ol **26a**

These results are fully in line with those reported for the urethane protected azetidinones, depicted in Scheme 3. The results shown in Table 2 can adequately be explained by steric approach control. The attacking nucleophile will preferentially approach the ketone from the least hindered (equatorial) face, resulting in the exclusive formation of the *syn* alcohol. The importance of steric factors is further demonstrated by the fact that the sterically demanding Grignards reagents, *e.g.* *iso*propylmagnesium bromide and *tert*-butylmagnesium bromide, do not result in any addition. Instead, reduction of the ketone is observed *via* a β-hydride transfer. For the sterically less demanding reagent methylmagnesium iodide apparently little steric repulsion is encountered during axial attack, in the case of the azetidin-3-one **5** with the small methyl substituent. As a result, this reaction lacks selectivity.

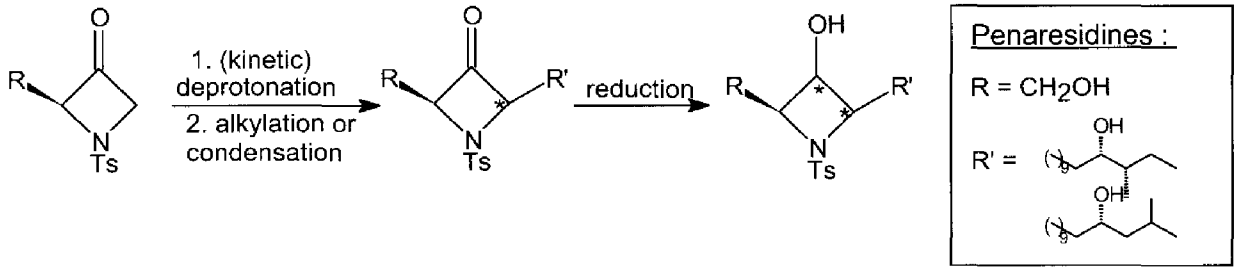
The substantial amount of axial attack in the case of allylmagnesium bromide is not without precedent. Unlike many organomagnesium compunds, allyl Grignard reagents do not react *via* a four-centre transition state, but rather *via* a six-centre transition state in which the entering carbon atom is not bonded to magnesium[17]. In this way the steric bulk of the reagent is less effective leading to a considerable axial attack [17], especially in the case of the azetidin-3-ones **5** and **14**.

In summary, Grignard reactions with *N*-tosyl 2-substituted azetidin-3-ones usually proceed with excellent stereoselectivity, analogous to azetidin-3-ones with an urethane-type substituent at nitrogen. These high selectivities can readily be explained in terms of steric approach control.

3.4 Deprotonation-Alkylation of 2-substituted azetidin-3-ones

Many of the naturally occurring functionalised azetidines are tri-substituted structures, *e.g.* the Penaresidines **2**. Alkylation or condensation of appropriate 2-substituted azetidin-3-ones constitutes an attractive way to introduce a third substituent in these four-membered nitrogen heterocycles (scheme 4).

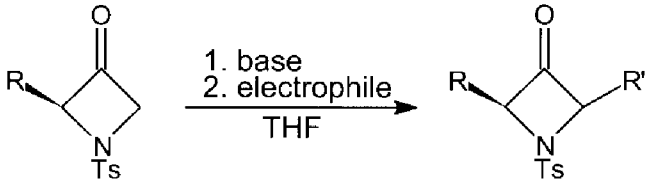
Scheme 4 *Potential synthesis of poly-functionalised 3-hydroxy azetidines from 2-substituted azetidin-3-ones*

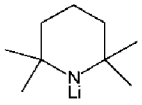


In order to validate this proposed synthetic methodology, the deprotonation and subsequent alkylation or condensation of simple alkyl substituted azetidin-3-ones was investigated.

In the early 1970s it became known that heating of *N*-diphenylmethyl-azetidin-3-one in methanol easily produces its dimer *via* selfcondensation[18]. Similarly, heating of this compound in the presence of benzaldehyde gave the corresponding aldol adduct in 43% yield[18]. However, an attempted reaction of azetidin-3-one **5** with benzaldehyde under those conditions did *not* lead to any new product. Experiments of azetidin-3-ones in deuterated methanol (MeOD), performed in a NMR tube, revealed the reason for the failure of this reaction. It appeared that the ketone is converted into the corresponding hemiacetal by addition of methanol to the carbonyl group. In this manner, the α-protons adjacent to the carbonyl group are no longer acidic and an aldol condensation cannot take place anymore. It remains unclear why such hemiacetal formation does not take place in the case of *N*-diphenylmethyl-azetidin-3-one.
The desired alkylation and condensation reactions should be possible by initial deprotonation of the substrate using a strong base. The results of the attempted kinetic deprotonations are collected in Table 3.

Table 3 *Attempted kinetic deprotonation and subsequent alkylation/condensation of* **5**



base	electrophile	conditions	result
iPr$_2$NLi	PhCHO	-78° - rt	decomposition
iPr$_2$NLi	MeI	-78° - rt	reduction
(Me$_3$Si)$_2$NLi	MeI	-78° - rt	decomposition
(Me$_3$Si)$_2$NLi	D_2O	-78° - rt	decomposition
	MeI	-78° - rt	decomposition
NaH	MeI	-78° - rt	decomposition
NaH	D_2O	-78° - rt	decomposition
iPr$_2$NEt	PhCHO	rt	no reaction
NaOH[a]	BnBr	rt	benzyl tosyl sulphone

[a] PTC conditions, using 2 mol% of triethylbenzylammonium cloride as the catalyst

None of these attempts was successful, either complete decomposition of the starting material was observed or reduction of the ketone group when the combination lithium di*iso*propylamide (LDA) and methyl iodide was used. Reduction of sterically hindered ketones by LDA by a β-hydride transfer has several precedents[19]. Other bases incapable of such β-hydride transfer, such as lithium hexamethyldisilazane and lithium 2,2,6,6-tetramethylpiperidine, did not result in a controlled reaction, as only decomposition was observed. The same holds for sodium hydride as a base. Weaker bases, such as *N,N*-di*iso*propyl-ethylamine, did not alter the pattern as no reaction was observed. Under two-phase conditions[20] detosylation took place as was apparent from the isolation of benzyl tosyl sulphone.

The unfortunate conclusion of these experiments is that the desired deprotonation/alkylation or condensation sequence as shown in Scheme 4 cannot be realised, neither using kinetically controled deprotonation nor under thermodynamically controled conditions.

3.5 Concluding remarks

The results described in this chapter lead to the conclusion that the high expectations with regard to the synthetic potential of 2-substituted azetidin-3-ones are not met in practice. The reduction of the carbonyl group can only be performed with high stereoselectivity for the substrate with a *tert*-butyl group as 2-substituent. In other cases the stereoselectivity is disappointingly low. Grignard reactions with these azetidin-3-ones however, proceed with complete stereoselectivity and give the tertiary alcohols in excellent chemical yield. This stereochemical result can be readily explained by invoking steric approach control. The attempted deprotonation and alkylation/condensation sequence failed under the conditions used.

3.6 Experimental Part

General remarks

Melting points were determined using a Reichert thermopan microscope and are uncorrected. Optical rotations were measured with a Perkin Elmer automatic polarimeter, model 241 MC, using concentrations *c* in g/100 ml at 20 °C in the solvents indicated. ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AC 100 (100 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer. The chemical shift δ is given in ppm relative to the internal standard (TMS for ^{1}H-NMR, $CDCl_3$ for ^{13}C-NMR). IR spectra were recorded on a Perkin Elmer 298 spectrophotometer. The wavenumber ν is listed in cm^{-1}. For (high resolution) mass spectra a double focussing VG7070E mass spectrometer was used. GC-MS were

measured using a Varian Saturn II GC-MS by on-column injection (DB-1 column, length 30 m, internal diameter 0.25 mm, film thickness 0.25 μm). Elemental analyses were performed using a Carlo Erba Instruments CHNS-O EA 1108 element analyzer.

Chemicals

THF was pre-distilled from calcium hydride, and prior to use distilled from sodium/benzophenone. Hexane, ethyl acetate were distilled from calcium hydride and stored over 4 Å molsieves. L-Selectride was used as a commercially available 1 M solution in THF. Lithium hexamethyldisilazane was used as a commercially available 1M solution in hexanes. Lithium di*iso*propylamide and lithium 2,2,6,6-tetramethylpiperidine were prepared by deprotonation of the corresponding secondary amines with *n*BuLi. All Grignard reagents were used as comercial available solution in either diethyl ether or THF. All other reagents were analytic grade and used as such.

Reduction experiments

Lithium aluminium *hydride reductions : general procedure 1(GP1)*

To a suspension of $LiAlH_4$ (1.1 equiv.) in dry THF, a solution of the appropriate azetidin-3-one in THF was added dropwise. After stirring at room temperature for 1 h the reaction was quenched with a saturated aqueous NH_4Cl solution. The mixture was extracted with Et_2O (3 x) and the combined organic layers washed with a saturated aqueous NaCl solution, dried over $MgSO_4$ and concentrated *in vacou*.

(3*S*) and (3*R*) 2-Methyl-1-tosyl-azetidin-3-ol **8a and 8b**

(S)-2-Methyl-1-(tosyl)-azetidin-3-one **5** (101 mg, 0.4 mmol) was treated according to GP1. crystallisation from hexane/ethyl acetate gave **8** (57 mg, 56%) as a white solid, consisting of inseparable diasteroisomers **8a** and **8b** (1:4), mp 98-112°C. **8a** (*minor isomer*): ^{1}H NMR (400 MHz, $CDCl_3$, 310K): δ 1.35 (d, , ^3J = 6.6 Hz, 3H, CH_3), 2.03 (br s, 1H , O*H*), 2.47 (s, 3H, $CH_3C_6H_4$), 3.61 (dd, J_{AB} = 9.6 Hz, ^3J = 2.8 Hz, 1H, NC(*H*)H), 3.83 (dd, J_{AB} = 9.6 Hz, ^3J = 6.7 Hz, 1H, NC(H)*H*), 4.09 (dq, 1H, $^3J_{2,3}$ = 6.7 Hz, 1H, C*H*CH$_3$,), 4.20 (ddd, J = 2.9 Hz and 6.6 Hz, 1H, C*H*(OH), J 2.8 en 6.7 Hz), 7.33 (dd, J = 8.1 Hz 2H, C_6H_4), 7.71 (dd, J = 8.1 Hz 2H, C_6H_4). **8b** (*major isomer*) ^{1}H NMR (400 MHz, $CDCl_3$, 310K): δ 1.40 (d, ^3J = 6.3 Hz, 3H, CH_3,), 2.03 (br s, 1H, O*H*), 2.47 (s, 3H, $CH_3C_6H_4$), 3.28 (dd, J_{AB} = 7.2 Hz, ^3J = 6.8 Hz, 1H, NC(*H*)H), 3.66 (dq., $^3J_{2,3}$ = 5.6 Hz, 1H, C*H*CH$_3$), 3.91 (dd, J_{AB} = 7.0 Hz, ^3J = 7.3 Hz, 1H, NC(H)*H*), 4.04 (ddd, J = 6.2 Hz, 1H, C(*H*)OH), 7.35 (dd, J = 8.1 Hz 2H, C_6H_4), 7.70 (dd, J = 8.1 Hz 2H, C_6H_4). IR ($CHCl_3$): ν 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2) cm^{-1}. MS (EI): *m/z*(%) 242 (0.14) [M+], 198 (64), 184 (11), 155 (83), 139 (2), 91 (100) [tropilium], 86 (5), 65 (26), 56 (13), 51 (4), 39 (12), 28 (18).

(3*S*) and (3*R*) 2-*iso*Propyl-1-tosyl-azetidin-3-ol **9a and 9b**

(S)-2-*iso*Propyl-1-(tosyl)-azetidin-3-one **6** (102 mg, 0.3 mmol) was treated according to GP1. Crystallisation from hexane/ethyl acetate gave **9** (69 mg, 67%) as a white solid consisting of inseparable diasteromers **9a** and **9b** (2:1), mp. 112-115° C. ^{1}H NMR (400 MHz, $CDCl_3$, 310 K)

δ: **9a** (*minor isomer*) : 0.96 (2xd, ^3J = 6.8 Hz, 6H CH(CH_3)$_2$), 2.19 (m, 1H, C*H*(CH$_3$)$_2$), 2.37 (s, 3H, $CH_3C_6H_4$), 3.58 (dd, *J* = 4.8 and 10.0 Hz, 1H NC*H*(H)), 3.80 (dd, *J* = 7.4 Hz, 1H C*Hi*Pr), 3.93 (dd, *J* = 7.4 and 10.0 Hz, NCH(*H*)), 4.23 (m, 1H, C*H*OH), 7.26 (d, *J* = 7.7 Hz, 2H, arom.), 7.65 (d, *J* = 7.7 Hz, 2H, arom.). **9b** (*major isomer*) : 0.91 (2xd, ^3J = 6.8 Hz, 6H, CH(CH_3)$_2$), 1.94 (m, 1H, C*H*(CH$_3$)$_2$), 2.37 (s, 3H, $CH_3C_6H_4$), 3.28 (dd, J_{AB} = 8.4 Hz, ^3J = 5.7 Hz, 1H, NC*H*(H)), 3.46 (dd, *J* = 5.4 Hz, 1H, C*Hi*Pr), 3.81 (dd, *J* = 8.0 Hz, 1H NCH(*H*)), 4.10 (ddd, *J* = 5.7 Hz, 1H, C*H*OH), 7.26 (d, *J* = 7.7 Hz, 2H, arom.), 7.65 (d, *J* = 7.7 Hz, 2H, arom.).IR ($CHCl_3$) ν: 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2) cm-1. MS (EI): *m/z* (%) 270 (15, M+), 252 (13), 226 (94), 184 (37), 155 (98), 139 (31), 114 (16), 91 (100), 84 (23), 65 (39), 55 (15), 41 (29), 28 (36).

(3*S*) and (3*R*) 2-*tert*-Butyl-1-tosyl-azetidin-3-ol **10a and 10b**

(S)-2-*tert*-Butyl-1-(tosyl)-azetidin-3-one **7** (100 mg, 0.36 mmol) was treated according to GP1. Crystallisation from hexane/ethyl acetate gave **10** (80 mg, 79%) as a white solid consisting of the inseparable diasteromers **10a** and **10b** (15:1).

The mixture of diastereomeric alcohols was dissolved in pyridine (5 ml) and the solution cooled in ice. Then 3,5-dinitrobenzoylchloride (194 mg, 1 equiv.) was added and the yellow solution was stirred for 12 h during which the temperature was allowed to rise to ambient. The reaction mixture was diluted with dichloromethane (5 ml) and washed with water. The organic layer was washed with 1N aqueous HCl (2x5ml), water (5 ml) and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. The obtained diastereoisomeric esters were separated by column chromatography (heptane : ethyl acetate 4:1).

(3S) (2-tert-Butyl-1-tosyl-azetidin-3-yl)-3',5'-dinitrobenzoate **10a'** *(major isomer)*

mp 140-141 °C. ^{1}H NMR (400 MHz, $CDCl_3$,) δ: 1.18 (s, 9H, C(C*H*$_3$)$_3$), 2.49 (s, 3H, C*H*$_3$C$_6$H$_4$), 3.96 (dd, *J* = 6.3 and 10.8 Hz, 1H, NC*H*(H)), 4.05 (d, $^3J_{2,3}$ = 8.3 Hz, 1H, C*H*tBu), 4.26 (dd, *J* = 8.3 and 10.8 Hz, 1H, NCH(*H*)), 5.37 (ddd, *J* = 6.3 and 8.2 Hz, 1H, C*H*O), 7.41 (d, *J* 8.1 Hz, 2H, C_6H_4), 7.81 (d, *J* 8.1 Hz, 2H, C_6H_4), 9.11 (s, 2H, H_{Ar} ortho), 9.25 (s, 1H, H_{Ar} para). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 21.7 ($CH_3C_6H_4$), 26.7 (C(CH$_3$)$_3$), 34.3 (*C*(CH$_3$)$_3$), 56.3 (NCH_2), 67.3 (CH*t*Bu), 75.3 (*C*HO), 122.9 (C_{Ar}H), 128.3 (C_{Ar}H), 129.3 (C_{Ar}H), 130.0 (C_{Ar}H), 132.6 (C_{Ar}), 132.9 (C_{Ar}), 144.6 (C_{Ar}), 148.8 (C_{Ar}), 161.7 (*C*=O).

(3R) (2-tert-Butyl-1-tosyl-azetidin-3-yl)-3',5'-dinitrobenzoate **10b'** *(minor isomer)*

^{1}H NMR (400 MHz, $CDCl_3$,) δ: 1.05 (s, 9H, C(C*H*$_3$)$_3$), 2.35 (s, 3H, C*H*$_3$C$_6$H$_4$), 3.74 (dd, *J* = 4.1 and 10.7 Hz, 1H, NC*H*(H)), 3.92 (d, $^3J_{2,3}$ = 4.1 Hz, 1H, C*H*tBu), 4.21 (dd, *J* = 6.5 and 10.4Hz, 1H, NCH(*H*)), 5.15 (ddd, *J* = 4.1 and 6.3 Hz, 1H, C*H*O), 7.37 (d, *J* 8.1 Hz, 2H, C_6H_4), 7.78 (d, *J* 8.1 Hz, 2H, C_6H_4), 8.89 (s, 2H, H_{Ar} ortho), 9.24 (s, 1H, H_{Ar} para). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 21.5 ($CH_3C_6H_4$), 25.3 (C(CH$_3$)$_3$), 33.1 (*C*(CH$_3$)$_3$), 55.0 (NCH_2), 67.0 (CH*t*Bu), 78.6 (CHO), 122.8 (C_{Ar}H), 128.5 (C_{Ar}H), 129.2 (C_{Ar}H), 129.7 (C_{Ar}H), 132.5 (C_{Ar}), 132.8 (C_{Ar}), 144.3 (C_{Ar}), 148.7 (C_{Ar}), 161.2 (*C*=O).

L-Selectride reductions : general procedure 2(GP2)

To a solution of the appropriate azetidin-3-one in dry THF under argon at -78° C, 1M L-Selectride in THF (1.1 eq.) was slowly added. After warming to room temperature the

solution was stirred for 3 h and then quenched with a mixture of H_2O/EtOH/10% NaOH/30% H_2O_2 (1:3:5:3 (v/v)). The mixture was extracted with Et_2O (3 x) and the combined organic layers washed with a saturated NaCl solution, dried over $MgSO_4$ and concentrated *in vacuo*.

(S)-2-Methyl-1-tosyl-azetidin-3-ol **8**
(S)-2-Methyl-1-(tosyl)-azetidin-3-one **5** (103mg, 0.4 mmol) was treated according to GP2. Crystallisation from hexane/ethyl acetate gave **8** (98 mg, 93%) as a white solid consisting of the inseparable diasteromers **8a** and **8b** (3:1).

(S)-2-*iso*Propyl-1-(tosyl)-azetidin-3-ol **9**
(S)-2-*iso*Propyl-1-(tosyl)-azetidin-3-one **6** (102 mg, 0.3 mmol) was treated according to GP2. Crystallisation from hexane/ethyl acetate gave **9** (69 mg, 67%) as a white solid consisting of the inseparable diasteromers **9a** and **9b** (1.2:1).

(3*S*) and (3*R*) 2-*tert*-Butyl-1-tosyl-azetidin-3-ol **10a and 10b**
(S)-2-*tert*Butyl-1-tosyl-azetidin-3-one **7** (101 mg, 0.36 mmol) was treated according to GP2. Crystallisation from hexane/ethyl acetate gave **10a** (93 mg, 91%) as a single diastereomer.

Grignard experiments

General procedure (GP3)
To a solution of the appropriate azetidin-3-one in dry THF (1 ml) was added at room temperature, a solution of the Grignard reagent (2 equiv.) using a syringe. After stirring for 1.5 h the reaction was quenched by addition of a saturated aqueous NH_4Cl solution. The mixture was extracted with Et_2O (3 x 15 ml) and the combined organic layers were washed with a saturated NaCl solution (3 x 10 ml), dried over $MgSO_4$ and concentrated *in vacuo*.

(2S,3S) and (2S,2R) 2,3-Dimethyl-1-tosyl-azetidin-3-ol **16a and 16b**
(S)-2-Methyl-1-(tosyl)-azetidin-3-one **5** (107 mg, 0.4 mmol) was treated according to GP3, to give **16** (83 mg, 73%) as a colourless oil consisting of a inseparable mixture of diastereomers (1:1). $[a]_D^{20}$ +40.1° (c=1 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *isomer 1:* δ 1.25 (d, *J* = 6.5 Hz, 3H, CHC*H*$_3$,), 1.31 (s, 3H, C*H*3COH), 2.39 (s, 3H, C*H*$_3$C$_6$H$_4$), 3.27 (d, *J* = 7.6 Hz, 1H, NC*H*(H),), 3.49 (d, *J* = 7.6 Hz 1H, NCH(*H*),), 3.69 (q, *J* = 6.5 Hz, 1H, C*H*CH$_3$,), 7.28-7.67 (m, 4H, C$_6$H$_4$). *isomer 2:* δ 0.97 (s, 3H, C*H*$_3$COH), 1.21 (d, *J* = 6.5 Hz, 3H, CHC*H*$_3$,), 2.39 (s, 3H, C*H*$_3$C$_6$H$_4$), 3.45 (d, *J* = 9.0 Hz, 1H, NC*H*(H)), 3.59 (d, *J* = 9.1 Hz, 1H, NCH(*H*)), 3.58 (q, *J* = 6.5 en 6.2 Hz, 1H, C*H*CH$_3$) 7.28-7.67 (m, 4H, C6H4). IR ($CHCl_3$): υ 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2). MS (EI): *m/z* (%) : 256 (13) [M+1], 155 (93) [Ts] 91 (100) [tropilium].

(2S,3S) 2-Methyl-3-vinyl-1-tosyl-azetidin-3- ol **17a**
(S)-2-Methyl-1-(tosyl)-azetidin-3-one **5** (100 mg, 0.4 mmol) was treated according to GP3. Crystallisation from hexane/ethyl acetate gave **17a** (120 mg, 95%) as a colourless oil. $[a]_D^{20}$ +39.2° (c=1 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (d, *J* = 6.5 Hz, 3H, C*H*$_3$,), 2.39

(s, 3H, $CH_3C_6H_4$), 3.60 (dd, J_{AB} =9.0 Hz, 2H, NCH_2), 3.82 (q, J = 6.5 Hz, 1H, $CHCH_3$,), 4.97 (2xd, J = 11.2 en 17.7 Hz, 2H, $CHCH_2$), 5.49 (dd, J = 10.8 en 17.3 Hz, 1H, $CHCH_2$,), 7.30 (d, J = 8.1 Hz, 2H, C_6H_4), 7.65 (d, J = 8.1 Hz, 2H, C_6H_4). IR ($CHCl_3$): υ 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2). MS (EI): *m/z* (%) : 268 (2) [M+1], 198 (90), 155 (94) [Ts], 91 (100) [tropilium).

(2S,3S) and (2S,3R) 3-Allyl-2-methyl-1-tosyl-azetidin-3- ol **18**

(S)-2-Methyl-1-(tosyl)-azetidin-3-one **5** (106 mg, 0.4 mmol) was treated according to GP3, to give **18** (89 mg, 71%) as a colourless oil consisting of a inseparable mixture of diastereomers (2:1). $[a]_D^{20}$ +36.7° (c=1 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *major isomer:* δ 1.24 (d, 3H, CH_3, J 6.6 Hz), 1.60 (s, 1H, O*H*), 1.92 (d, 2H, $CH_2CH=CH_2$, J 7.2 Hz), 2.39 (s, 3H, $CH_3C_6H_4$), 3.53 (d, 1H, NCH_2, J 9.2 Hz), 3.58 (d, 1H, NCH_2, J 9.8 Hz), 3.79 (q, 1H, NC*H*, J 6.5 Hz), 4.91 (d, 1H, $CH_2CH=CH_2$, J 7.1 Hz), 5.00 (d, 1H, $CH_2CH=CH_2$, J 10.1 Hz), 5.44 (sextet, 1H, $CH_2CH=CH_2$, J 7.2, 8.6 en 10.0 Hz), 7.28-7.67 (m, 4H, C_6H_4). *minor isomer:* δ 1.27 (s, 3H, CH_3), 2.05 (s, 1H, O*H*), 2.16 (s, 2H, $CH_2CH=CH_2$), 2.38 (s, 3H, $CH_3C_6H_4$), 3.18 (d, 1H, NCH_2, J 7.8 Hz), 3.60 (d, 1H, NCH_2, J 8.9 Hz), 3.65 (q, 1H, NC*H*, J 6.6 Hz), 5.15 (d, 1H, $CH_2CH=CH_2$, J 12.6 Hz), 5.18 (d, 1H, CH2CH=CH_2, J 9.3 Hz), 5.72 (sextet, 1H, CH2C*H*=CH_2, J 7.2, 8.6 en 10.4 Hz), 7.28-7.67 (m, 4H, C_6H_4). IR ($CHCl_3$): υ 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2). MS (EI): *m/z* (%) : 282 (14) [M^+], 198 (95), 155 (100) [Ts], 91 (87) [tropilium].

(2S,3S)-2-Methyl-3-phenyl-1-tosyl-azetidin-3-ol **19a**

(S)-2-Methyl-1-(tosyl)-azetidin-3-one **5** (110 mg, 0.5 mmol) was treated according to GP3. Crystallisation from hexane/ethyl acetate gave **19a** (37 mg, 25%) as a white solid. mp 140-141°C. $[a]_D^{20}$ +23.6° (c=1 in $CHCl_3$). ^{1}H NMR(400 MHz, $CDCl_3$): δ 1.37 (d, J = 6.5 Hz, 3H, CH_3,), 2.42 (s, 3H, $CH_3C_6H_4$), 3.81 (d, part of AB, J_{AB} = 9.1 Hz, 1H, NC*H*(H)), 3.92 (d, part of AB, J_{AB} = 9.1 Hz, 1H, NCH(*H*)), (4.13 (q, J = 6.4 Hz, 1H, $CHCH_3$), 6.89-6.91 (m, 3H, arom.), 7.15-7.20 (m, 2H, arom.), 7.32 (d, J = 8.1 Hz, 2H, C_6H_4), 7.70 (d, J = 8.1 Hz, 2H, C_6H_4). IR ($CHCl_3$): υ 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2). MS (EI): *m/z* (%) : 318 (7) [M+1], 198 (100), 134 (74), 155 (71) [Ts], 91 (86) [tropilium]. $C_{17}H_{19}NO_3S$ (317.40) C 64.33 H 6.03 N 4.41 found C 63.96 H 5.80 N 4.48.

(2S,3S)-2-Benzyl-3-methyl-1-tosyl-azetidin-3-ol **20a**

(S)-2-Benzyl-1-(tosyl)-azetidin-3-one **14** (104 mg, 0.3 mmol) was treated according to GP3 to give **20a** (80 mg, 73%) as a colourless oil. $[a]_D^{20}$ +82.5° (c=1 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 3H, CH_3), 2.46 (s, 3H, $CH_3C_6H_4$), 3.02 (dd, part of AB, J_{AB} = 15.2 Hz, ^3J = 10.6 Hz, 1H, CH_2Ph,), 3.29 (dd, part of AB, J_{AB} = 15.2 Hz, ^3J = 4.2 Hz, 1H, CH_2Ph,), 3.33 (d, part of AB, J_{AB} = 7.6 Hz, 1H, NC*H*(H)), 3.57 (d, part of AB, J_{AB} = 7.6 Hz, 1H, NCH(*H*)), 3.84 (dd, J = 4.1 and 10.6 Hz, 1H, *CH*Bn), 7.19-7.26 (m, 5H, C_6H_5), 7.36 (d, J = 8.1 Hz, 2H, C_6H_4), 7.68 (d, J = 8.1 Hz, 2H, C_6H_4). IR ($CHCl_3$): υ 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2). MS (EI): *m/z*(%) : 332 (0.4) [M+1], 155 (60) [Ts], 91 (100) [tropilium].

(2S,3S)-2-Benzyl-3-vinyl-1-tosyl-azetidin-3-ol **21a**

(S)-2-Benzyl-1-(tosyl)-azetidin-3-one **14** (101 mg, 0.3 mmol) was treated according to GP3 to give **21a** (96 mg, 94%) as a colourless oil. $[a]_D^{20}$ +69.5° (c=1 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ : 2.35 (s, 1H, O*H*), 2.45 (s, 3H, $CH_3C_6H_4$), 3.10 (dd, part of AB, J_{AB} = 14.1 Hz, ^3J = 3.9 Hz, 1H, CH_2Ph), 3.27 (dd, part of AB, J_{AB} = 14.1 Hz, ^3J = 10.8 Hz, 1H, CH_2Ph), 3.68 (dd, J_{AB} = 9.0 Hz, 2H, NCH_2), 3.98 (dd, J = 3.9 and 10.7 Hz, 1H, C*H*Bn), 4.83 (2xd, J = 9.5 and 17.0 Hz, 2H, $CH=CH_2$), 5.39 (dd, J = 17.2 Hz, 1H, $CH=CH_2$), 7.16-7.26 (m, 5H, C_6H_5.), 7.38 (d, J = 8.0 Hz, 2H, C_6H_4), 7.73 (d, J = 8.0 Hz, 2H, C_6H_4). IR (CHCl3): υ 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2). MS (EI): *m/z* (%) 344 (4) [M+], 274 (76), 155 (62) [Ts], 91 (100) [tropilium].

(2S,3S)-3-Allyl-2-benzyl-1-tosyl-azetidin-3-ol **22**

(S)-2-Benzyl-1-(tosyl)-azetidin-3-one **14** (103 mg, 0.3 mmol) was treated according to GP3 to give **22** (106 mg, 91%) as a colourless oil consisting of 2 inseparable diasteromers (2:1). $[a]_D^{20}$ +70.5° (c=1 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): *major isomer:* δ 1.77 (dd, J = 8.0 Hz, 2H, $CH_2CH=CH_2$), 2.13 (s, 1H, O*H*), 2.45 (s, 3H, $CH_3C_6H_4$), 3.08 (dd, part of AB, J_{AB} = 13.9 Hz, ^3J = 4.1 Hz, 1H, CH_2Ph), 3.28 (dd, part of AB, J_{AB} = 13.9 Hz, ^3J = 10.8 Hz, 1H, CH_2Ph), 3.58 (d, J_{AB} = 9.2 Hz, 1H, NC*H*(H)), 3.64 (d, J_{AB} = 9.2 Hz, 1H, NCH(*H*)), 3.94 (dd, J = 4.0 and 10.5 Hz, 1H, C*H*Bn), 4.78 (dd, J = 9.4 and 17.0 Hz, 2H, $CH_2CH=CH_2$), 5.00 (m, 1H, $CH_2CH=CH_2$), 7.19-7.26 (m, 5H, C_6H_5), 7.28-7.67 (m, 4H, C_6H_4). *minor isomer:* δ 1.96 (s, 1H, O*H*), 2.35 (dd, J = 6.8 and 13.9 Hz, 1H, $CH_2CH=CH_2$), 2.45 (s, 3H, $CH_3C_6H_4$), 2.75 (dd, J = 6.8 and 13.9 Hz, 1H, $CH_2CH=CH_2$), 3.09 (dd, part of AB, J_{AB} = 14.6 Hz, ^3J = 5.1 Hz, 1H, CH_2Ph), 3.29 (dd, part of AB, J_{AB} = 14.4 Hz, ^3J = 11.1 Hz, 1H, CH_2Ph), 3.64 (d, J_{AB} = 7.7 Hz, 1H, NCH_2), 3.73 (d, J_{AB} = 7.7 Hz, 1H, NCH_2), 3.97 (dd, J = 4.2 Hz, 1H, NC*H*), 5.19 (dd, J = 8.6 and 12.8 Hz, 2H, $CH_2CH=CH_2$), 5.75 (m, 1H, $CH_2CH=CH_2$), 7.19-7.26 (m, 5H, C_6H_5), 7.28-7.67 (m, 4H, C_6H_4). IR (CHCl3): υ : 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2). MS (EI): *m/z* (%) 358 (0.16) [M+], 274 (86), 155 (61) [Ts], 91 (100) [tropilium].

(2S,3S)-2-Benzyl-3-phenyl-1-tosyl-azetidin-3-ol **23a**

(S)-2-Benzyl-1-(tosyl)-azetidin-3-one **14** (101 mg, 0.3 mmol) was treated according to GP3. Crystallisation from *iso*propylether/hexane (10:1) gave **23a** (101 mg, 80%) as a white solid, mp. 137-139°C. $[a]_D^{20}$ +60.5° (c=1 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 1H, O*H*), 2.45 (s, 3H, $CH_3C_6H_4$), 3.21 (dd, part of AB, J_{AB} = 14.3 Hz, ^3J = 4.0 Hz, 1H, CH_2Ph), 3.48 (dd, part of AB, J_{AB} = 14.2 Hz, ^3J = 10.5 Hz, 1H, CH^2Ph), 3.96 (dd, J_{AB} = 9.2, 1H, NCH_2), 4.36 (dd, J = 4.0 and 10.4 Hz, 1H, C*H*Bn), 6.63 (d, J = 7.4 Hz, 2H, arom.), 7.19-7.26 (m, 7H, arom.), 7.36 (d, J = 8.2 Hz, 2H, C_6H_4), 7.75 (d, J = 8.2 Hz, 2H, C_6H_4). IR ($CHCl_3$): υ: 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2). MS (EI): *m/z* (%) 394 (1) [M+], 274 (60), 155 (38) [Ts], 91 (100) [tropilium]. $C_{23}H_{23}NO_3S$ (393.50) calc. C 70.20 H 5.89 N 3.56 found C 69.84 H 5.85 N 3.56.

(2S,3S)-2-*iso*Propyl-3-methyl-1-tosyl-azetidin-3-ol **24a**

(S)-2-*iso*Propyl-1-(tosyl)-azetidin-3-one **6** (103 mg, 0.4 mmol) was treated according to GP3. Crystallisation from *iso*propylether/hexane (10:1) gave **24a** (88 mg, 81%) as a white solid, mp. 123-128°C. $[a]_D^{20}$ +80.3° (c=1 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (d, J = 6.6 Hz,

3H, CH(CH_3)$_2$), 0.93 (s, 3H, CH_3), 1.01 (d, J = 6.6 Hz, 3H, CH(CH_3)^2), 2.06 (m, 1H, CH(CH$_3$)$_2$), 2.39 (s, 3H, $CH_3C_6H_4$), 3.31 (d, J = 9.2 Hz, 1H, CH*i*Pr), 3.62 (dd, J = 9.8 Hz, 1H, NCH_2), 7.38 (d, J = 8.0 Hz, 2H, C_6H_4), 7.73 (d, J = 8.0 Hz, 2H, C_6H_4). IR (CHCl3): υ 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2). MS (EI): *m/z* (%) : 284(6) [M+1], 226(100), 155(98). $C_{14}H_{21}NO_3S$ (283.38) calc. C 59.34 H 7.47 N 4.94 found C 59.20 H 7.44 N 5.00.

(2S,3S)-2-*iso*Propyl-3-vinyl-1-tosyl-azetidin-3-ol **25a**

(S)-2-*iso*Propyl-1-(tosyl)-azetidin-3-one **6** (107 mg, 0.4 mmol) was treated according GP3 to give **25a** (105 mg, 96%) as a colourless oil. $[a]_D^{20}$ +55.0° (c=1 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ : 0.78 (d, ^3J = 6.6 Hz, 3H, CH(CH_3)$_2$), 0.99 (d, ^3J = 6.6 Hz, 3H, CH(CH_3)$_2$), 2.13 (m, 1H, CH(CH$_3$)$_2$), 2.38 (s, 3H, $CH_3C_6H_4$), 2.68 (s, 1H, OH), 3.37 (d, ^3J = 9.2 Hz, 1H, CH*i*Pr), 3.66 (dd, J_{AB} = 9.9 Hz, 2H, NCH_2), 4.92 (dd, J = 2.9 and 7.6 Hz, 2H, CH=CH_2), 5.40 (dd, J = 10.5 Hz, 1H, CH=CH$_2$), 7.29 (d, J = 7.8 Hz, 2H, C_6H_4), 7.63 (d, J = 7.8 Hz, 2H, C_6H_4). IR (CHCl3): υ 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2). MS (EI): *m/z* (%) 296 (0.27) [M$^+$], 226 (100), 155 (85) [Ts], 91 (96) [tropilium].

(2S,3S)-3-Allyl-2-*iso*propyl-1-tosyl-azetidin-3-ol **26a**

(S)-2-*iso*Propyl-1-(tosyl)-azetidin-3-one **6** (101 mg, 0.4 mmol) was treated according to GP3. Crystallisation from *iso*propylether/hexane (10:1) gave **26a** (105 mg, 90%) as a white solid. mp. 90-91°C. $[a]_D^{20}$ +55.0° (c=1 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ : 0.91 (d, ^3J = 6.6 Hz, 3H, CH(CH_3)$_2$), 1.07 (d, ^3J = 6.6 Hz, 3H, CH(CH_3)$_2$), 1.90 (ddd, 2H, J_{AB} = 14.0 Hz, J = 7.6 Hz, 2H, CH_2CH=CH$_2$), 1.94 (s, 1H, OH), 2.12 (m, 1H, CH(CH$_3$)$_2$), 2.46 (s, 3H, $CH_3C_6H_4$), 3.48 (d, J = 9.0 Hz, 1H, CH*i*Pr), 3.70 (dd, J_{AB} = 9.9 Hz, 2H, NCH_2), 4.95 (dd, J = 1,8 and 17.1 Hz, 1H, CH_2CH=CH_2), 5.11 (dd, J = 1,9 and 10.2 Hz, 1H, CH_2CH=CH_2), 5.54 (m, J = 10.2 and 17.0 Hz, 1H, CH=CH$_2$), 7.38 (d, J = 8.0 Hz, 2H, C_6H_4), 7.73 (d, J = 8.0 Hz, 2H, C_6H_4). IR (CHCl3): υ 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2). MS (EI): *m/z* (%) 310 (0.13) [M+], 226 (93), 155 (81) [Ts], 91 (100) [tropilium]. $C_{16}H_{23}NO_3S$ (309.42) calcd. C 62.11 H 7.50 N 4.53 found C 62.20 H 7.83 N 4.66.

(2S,3S)-2-*iso*Propyl-3-phenyl-1-tosyl-azetidin-3-ol **27a**

(S)-2-*iso*Propyl-1-(tosyl)-azetidin-3-one **6** (101 mg, 0.4 mmol) was treated according to GP3. Crystallisation from *iso*propylether/hexane (10:1) gave **27a** (119 mg, 91%) as a white solid. mp. 135-142°C. $[a]_D^{20}$ +56.3° (c=1 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ : 0.87 (d, J = 6.7 Hz, 3H, CH(CH_3)$_2$), 1.14 (d, J = 6.7 Hz, 3H, CH(CH_3)$_2$), 1.61 (s, 1H, OH), 2.32 (m, 1H, CH(CH$_3$)$_2$), 2.45 (s, 3H, $CH_3C_6H_4$), 3.87 (dd, J_{AB} = 9.1 Hz, 2H, NCH_2), 4.10 (d, J = 9.9 Hz, 1H, CH*i*Pr), 6.93 (dd, J = 1.9 and 7.6 Hz, 2H, arom.), 7.17 (m, 3H, arom.), 7.38 (d, J = 8.0 Hz, 2H, C_6H_4), 7.73 (d, J = 8.0 Hz, 2H, C_6H_4). IR ($CHCl_3$): υ 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2). MS (EI): *m/z* (%) 240 (3), 226 (100), 155 (53) [Ts], 91 (73) [tropilium]. $C_{19}H_{23}NO_3S$ (345.45) calcd. C 66.06 H 6.71 N 4.05 found C 65.91 H 6.53 N 4.17.

(2S,3S)-2-(*tert*-Butyldiphenylsilyloxymethyl)-3-methyl-1-tosyl-azetidin-3-ol **28a**
(S)-2-(*tert*-Butyldiphenylsilyloxymethyl)-1-tosyl-azetidin-3-one **15** (107 mg, 0.2 mmol) was treated according to GP3 to give **28a** (107 mg, 95%) as a colourless oil. $[a]_D^{20}$ +54.0° (c=1 in $CHCl_3$). ^1H NMR (400 MHz, CDCl3): δ 0.84 (s, 3H, CH_3), 1.01 (s, 9H, $C(CH_3)_3$), 1.50 (s, 1H, O*H*), 2.38 (s, 3H, $CH_3C_6H_4$), 3.58 (d, part of AB, J_{AB} = 9.3 Hz, 1H, NCH_2), 3.62 (dd, *J* = 2.5 and 3.8 Hz, 1H, CH_2O), 3.85 (d, part of AB, J_{AB} = 9.3 Hz, 1H, NCH_2), 3.89 (dd, *J* = 2.4 and 11.6 Hz, 1H, CH_2O), 4.07 (dd, *J* = 4.1 and 11.6 Hz, 1H, $CHCH_2O$,), 7.19-7.26 (m, 10H, 2×Ph), 7.38 (d, *J* = 8.0 Hz, 2H, C_6H_4), 7.73 (d, *J* = 8.0 Hz, 2H, C_6H_4). IR ($CHCl_3$): υ 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2). MS (EI): *m/z* (%) 332 (0.40) [M+], 274 (87), 176 (18), 155 (60) [Ts], 132 (11), 91 (100) [tropilium].

(2S,3S)-2-(*tert*-Butyldiphenylsilyloxymethyl)-3-vinyl-1-tosyl-azetidin-3-ol **29a**
(S)-2-(*tert*-butyldiphenylsilyloxymethyl)-1-tosyl-azetidin-3-one **15** (100 mg, 0.2 mmol) was treated according to GP3 to give **29a** (87 mg, 83%) as a colourless oil. $[a]_D^{20}$ +57.1° (c=1 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (s, 9H, $C(CH_3)_3$), 2.38 (s, 1H, O*H*), 2.38 (s, 3H, $CH_3C_6H_4$), 3.68 (d, part of AB, J_{AB} = 9.3 Hz, 1H, NCH_2), 3.76 (dd, *J* = 2.9 and 5.3 Hz, 1H, CH_2O), 3.84 (d, part of AB, J_{AB} = 9.3 Hz, 1H, NCH_2), 3.90 (dd, *J* = 2.9 and 11.5 Hz, 1H, CH_2O), 4.11 (dd, *J* = 5.5 and 11.5 Hz, 1H, $CHCH_2O$), 4.94 (dd, *J* = 10.7 and 17.1 Hz, 2H, $CH=CH_2$), 5.33 (dd, *J* = 10.7 and 17.2 Hz1H, $CH=CH_2$), 7.19-7.26 (m, 10H, 2×Ph), 7.38 (d, *J* = 8.2 Hz, 2H, C_6H_4), 7.73 (d, *J* = 8.2 Hz, 2H, C_6H_4). IR ($CHCl_3$): υ 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2). MS (EI): *m/z* (%) : 464(79), 386(27), 199(100).

(2S,3S)-2-Allyl-2-(*tert*-butyldiphenylsiliyloxymethyl)-1-tosyl-azetidin-3-ol **30a**
(S)-2-(*tert*-butyldiphenylsilyloxymethyl)-1-tosyl-azetidin-3-one **15** (107 mg, 0.2 mmol) was treated according to GP3 to give **30a** (93 mg, 80%) as a colourless oil. $[a]_D^{20}$ +57.7° (c =1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.10 (s, 9H, $C(CH_3)_3$), 1.57 (s, 1H, O*H*), 1.72 (dd, part of AB, *J* = 7.3 en 14.0 Hz, 1H, $CH_2CH=CH_2$), 1.83 (dd, part of AB, *J* = 7.1 en 14.0 Hz, 1H, $CH_2CH=CH_2$), 2.46 (s, 3H, $CH_3C_6H_4$), 3.68 (d, part of AB, J_{AB} = 9.5 Hz, 1H, NCH_2), 3.74 (dd, *J* = 2.4 and 3.7 Hz, 1H, CH_2O), 3.87 (d, part of AB, J_{AB} = 9.3 Hz, 1H, NCH_2), 3.89 (dd, *J* = 3.5 and 10.9 Hz, 1H, CH_2O), 4.14 (dd, *J* = 4.2 and 11.6 Hz, 1H, $CHCH_2O$), 4.78 (dd, *J* = 17.1 Hz, 1H, $CH_2CH=CH_2$), 4.97 (dd, *J* = 10.2 Hz, 1H, $CH_2CH=CH_2$), 5.57 (m, 1H, $CH_2CH=CH_2$), 7.19-7.72 (m, 10H, 2×Ph), 7.38 (d, *J* = 8.2 Hz, 2H, C_6H_4), 7.73 (d, *J* = 8.2 Hz, 2H, C_6H_4). IR ($CHCl_3$): υ 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2). MS (EI): *m/z* (%) 520 (0.02) [M+], 478 (58), 199 (81), 155 (36) [Ts], 91 (100) [tropilium].

(2S,3S)-2-(*tert*-Butyldiphenylsilyloxymethyl)-3-phenyl-1-tosyl-azetidin-3-ol **31a**
(S)-2-(*tert*-Butyldiphenylsilyloxymethyl)-1-tosyl-azetidin-3-one **15** (106 mg, 0.2 mmol) was treated according to GP3 to give **31a** (95 mg, 97%) as a colourless oil. $[a]_D^{20}$ +52.7° (c=1 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ : 0.97 (s, 9H, $C(CH_3)_3$), 1.52 (br s, 1H, O*H*), 2.39 (s, 3H, $CH_3C_6H_4$), 3.94 (dd, *J* = 3.1 and 11.3 Hz, 1H, CH_2O), 3.97 (dd, *J* = 9.2 Hz, 2H, NCH_2), 4.07 (dd, *J* = 3.0 and 6.1 Hz, 1H, CH_2O), 4.22 (dd, *J* = 6.1 and 11.3 Hz, 1H, $CHCH_2O$), 6.81-7.65 (m, 19H,

3xPh and C_6H_4). IR ($CHCl_3$): υ 3400-3300 (OH), 3000-2800 (alkyl), 1350 (SO2). MS (EI): *m/z* (%) : 514(42), 199(89), 91(100).

Deprotonation experiments

Kinetic deprotonations (general procedure)

To a cooled (-78 °C) solution of the azetidin-3-one, a pre-cooled solution of the appropriate base (1 equiv.) was added dropwise. The solution was stirred at this temperature for 20 min and then the electrophile (see Table 3) was added. The temperature was allowed to rise to ambient and the resulting dark mixture was subsequently quenched by addition of an excess of saturated aqueous ammonium chloride. The water layer was extracted with ether (2x) and the combined organic layer dried over $MgSO_4$ and concentrated *in vacuo*. The residu was chromatographed over silica, however no identifiable product was isolated.

Deprotonation under PTC conditions

(S)-2-methyl-1-(tosyl)-azetidin-3-one **5** (1.0 g, 3.7 mmol) and tetrabutylammonium chloride (2 mol%) were dissolved in 10 ml 50% aqueous NaOH. Benzyl bromide (2.0 g, 3 equiv.) was added and the mixture stirred at ambient temperature. After 5 h the yellow mixture was extracted with ether (3x), the combined extracts dried over $MgSO_4$ and concentrated *in vacuo*. The residu was chromatographed over silica (hexane : ethyl acetate 4:1 (v/v)) to give benzyl tolyl sulphone. ^1H NMR (100 MHz, $CDCl_3$) : δ 2.32 (s, 3H, CH_3), 4.20 (s, 2H, CH_2Ph), 6.98-7.45 (m, 9H, arom.). IR ($CHCl_3$) : ν (cm^{-1}) 1315, 1150. MS (EI) *m/z* (%) : 246 (3) [M^+], 182 (7), 139 (6), 91 (100).

3.7 Crystal structure data

(3S) (2-tert-butyl-1-tosyl-azetidin-3-yl)-3',5'-dinitrobenzoate **10a'**

Crystals of **10a'** suitable for X-ray diffraction studies were obtained by recrystallisation from heptane : dichloromethane = 3 : 1 . A single crystal was mounted in air on a glass fibre. Intensity data were collected at room temperature. An Enraf-Nonius CAD4 single-crystal diffractometer was used, Mo-Kα radiation, Θ-2Θ scan mode. Unit cell dimensions were determined from the angular setting of 25 reflections. Intensity data were corrected for Lorentz and polarization effects.Semi-empirical absorption correction (psi-scans)[22] was applied. The structure was solved by the program CRUNCH[23] and was refined with standard methods (refinement against F^2 of all reflections with SHELXL97[24] with anisotropic parameters for the nonhydrogen atoms. All hydrogen atoms were initially placed at calculated positions and were freely refined subsequently. A structure determination summary is given in Table 4.

Table 4 Crystal data and structure refinement for compound **10a'**

Empirical formula:	$C_{21}H_{23}N_3O_8S$
Colour/ shape:	colourless transparent / rough fragment
Formula weightt	477.48 g mol^{-1}
Temperature:	293(2) K
Wavelength:	0.71073 Å
Crystal system	Orthorhombic
Space group:	$P2_1$
Unit cell dimensions:	a = 10.5445(10) Å α = 90°
	b = 19.666(2) Å β = 90°
	c = 10.7305(13) Å γ = 90°
Volume:	2225.1(4) $Å^3$
Z:	4
Density (calculated):	1.425 kg .m^{-3}
Absorption coefficient:	0.199 mm^{-1}
F (000):	1000
Crystal Size:	0.36 x 0.33 x 0.25 mm
Θ range for data collection:	2.71 to 26.30°
Index ranges:	$-13 \le h \le 13$, $0 \le k \le 24$, $0 \le l \le 13$
Reflections collected/unique:	4876 / 4513 [R_{int} = 0.0423]
Reflections observed:	3417 ([$I_o > 2\sigma(I_o)$])
Refinement method:	Full-matrix least-squares on F^2
Data / restraints / parameters:	4513 / 0 / 390
Goodness-of-fit on F^2:	1.075
Final R indices [$I > 2\sigma(I)$]:	R_1 = 0.0460, wR_2 = 0.1022
R indices (all data):	R_1 = 0.0714, wR_2 = 0.1133
Largest diff. peak and hole:	0.231 and -0.222 e.$Å^{-3}$

(2S,3S)-3-Allyl-2-isopropyl-1-tosyl-azetidin-3-ol **26a**

Crystals of **26a** suitable for X-ray diffraction studies were obtained by recrystallisation from heptane : dichloromethane = 3 : 1 . A single crystal was mounted in air on a glass fibre. Intensity data were collected at room temperature. An Enraf-Nonius CAD4 single-crystal diffractometer was used, Mo-Kα radiation, Θ-2Θ scan mode. Unit cell dimensions were determined from the angular setting of 25 reflections. Intensity data were corrected for Lorentz and polarization effects.Semi-empirical absorption correction (psi-scans)[22] was applied. The structure was solved by the program CRUNCH[23] and was refined with standard methods (refinement against F^2 of all reflections with SHELXL97[24] with anisotropic parameters for the nonhydrogen atoms. All hydrogen atoms were initially placed at calculated positions and were freely refined subsequently. A structure determination summary is given in Table 5

Table 5 Crystal data and structure refinement for compound **26a**

Empirical formula:	$C_{16}H_{23}NO_3S$
Colour/ shape:	colourless transparent / regular fragment
Formula weight	309.41 g mol^{-1}
Temperature:	208(2) K
Wavelength:	1.54184 Å
Crystal system	Orthorhombic
Space group:	$P2_1$
Unit cell dimensions:	a = 6.2646(2) Å α = 90°
	b = 11.6402(4) Å β = 90°
	c = 22.4569(9) Å γ = 90°
Volume:	1637.60(10) $Å^3$
Z:	4
Density (calculated):	1.255 kg .m^{-3}
Absorption coefficient:	1.834 mm^{-1}
F (000):	664
Crystal Size:	0.25 x 0.17 x 0.12 mm
Θ range for data collection:	3.94 to 69.91°
Index ranges:	$-7 \le h \le 0$, $0 \le k \le 14$, $-27 \le l \le 0$
Reflections collected/unique:	1818 / 1818 [R_{int} = 0.0423]
Reflections observed:	1731 ([$I_o > 2\sigma(I_o)$])
Refinement method:	Full-matrix least-squares on F^2
Data / restraints / parameters:	1818 / 0 / 282
Goodness-of-fit on F^2:	1.070
Final R indices [$I > 2\sigma(I)$]:	R_1 = 0.0292, wR_2 = 0.0775
R indices (all data):	R_1 = 0.0313, wR_2 = 0.0793
Largest diff. peak and hole:	0.155 and -0.419 e.$Å^{-3}$

3.8 References

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4 A new synthesis of 1,3-oxazolidin-5-ones

4.1 Introduction

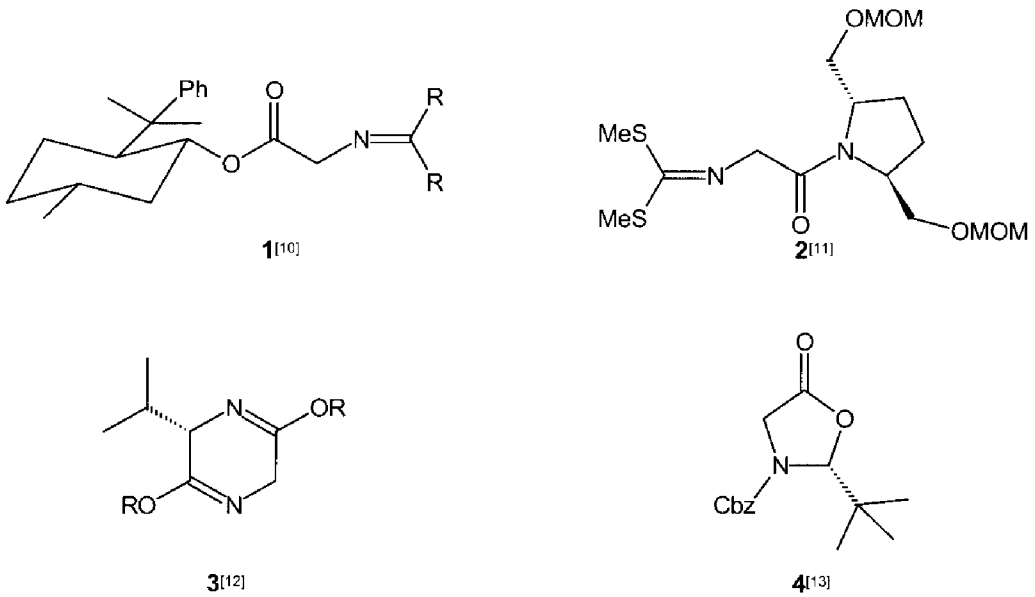
α-Amino acids belong to one of the five major classes of natural products and they exhibit important and diverse biological functions, *e.g.* constituent of peptides and proteins, neuronal signal transduction, *etc.*[1,2]. Besides the 20 proteinogenic amino acids, there are at least 700 naturally occurring unusual, non-proteinogenic, amino acids[3]. Many of these are produced by micro-organisms and many of them interfere with biochemical pathways of other organisms. Man-designed unusual amino acids have found application in both pharmaceutical and agricultural areas. Especially α-alkylated α-amino acids are of interest, because their incorporation into proteins often leads to modified and conformationally constrained backbone conformations[4] with increased lipophilicity[5] and enhanced resistance to both enzymatic and chemical hydrolysis[6].

Numerous methods of preparation of optically pure α-amino acids have been developed over the past decades. These synthetic achievements have been reviewed comprehensively[7]. There are two major ways to achieve the asymmetric synthesis of α-amino acids, *viz.* resolution of racemates and stereoselective synthesis. In industry until present the first approach is most frequently used. The racemic synthesis can readily be accomplished using the Strecker synthesis[8] and the kinetic (enzymatic) resolution may be combined with racemisation of the unwanted stereoisomer, allowing the synthesis of α-amino acids in 100% yield/100% e.e. (asymmetric transformation)[9]. In academia, the challenging stereoselective synthesis receives most attention. For this four approaches can be recognised : *i.* enantioselective introduction of the α-hydrogen, *ii.* enantioselective introduction of the α-amino function, *iii.* asymmetric Strecker synthesis and *iv.* stereoselective introduction of the side-chain(s).

The last mentioned approach, that has received considerable attention, is generally based on the highly diastereoselective reaction of chiral glycine α-anion equivalents

with electrophiles. Many of these chiral glycine derivatives have been developed, some of which are depicted in Figure 1.

Figure 1 *Some chiral glycine equivalents*



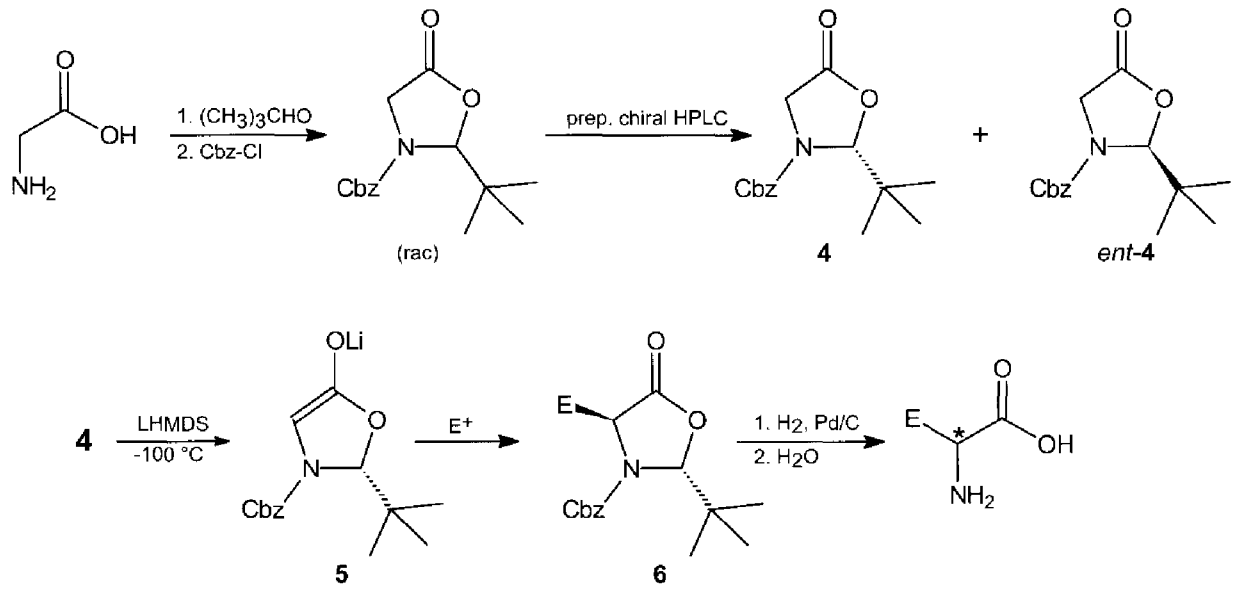
1[10] **2**[11] **3**[12] **4**[13]

Ideally, chiral glycine equivalents should have the following properties: ready accessibility of both enantiomers, high reactivity in C-C bond-forming reactions, high diastereoselectivity during further transformations and easy conversion of the products into the free amino acids in such a manner that no purification by ion-exchange chromatography is required[13]. Most of the developed systems partly meet these requirements. The final step usually is an acid or alkaline hydrolysis, necessitating a separation from the salts. A positive exception to this is the 1,3-oxazolidin-5-one **4**, which will be discussed in somewhat more detail in the next section.

4.2 1,3-Oxazolidin-5-ones as chiral glycine equivalent

The 1,3-oxazolidin-5-one **4** meets all the requirements of an ideal chiral glycine equivalent. Both enantiomers are available through a resolution of the readily available racemate by means of preparative chiral HPLC[13,14]. Deprotonation of **4** generates an enolate which reacts with electrophiles in a highly diastereoselective fashion (d.e.>98%). The electrophile preferentially attacks the face of the enolate *anti* with respect to the bulky *t*Bu-substituent. Subsequent removal of the benzyloxycarbonyl group by catalytic hydrogenolysis gives an unstable aminal, which spontaneously undergoes hydrolysis upon the addition of water to give the desired amino acid under salt-free conditions (scheme 1).

Scheme 1 *Synthesis of 1,3-oxazolidin-5-ones* **4** *and its application as chiral glycine equivalent*



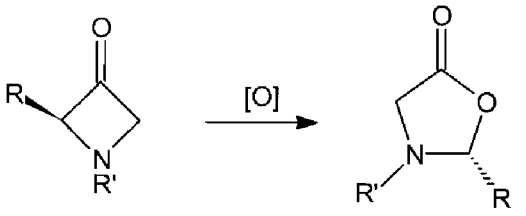
Although the application of oxazolidinone **4** is attractive in many respects, there are a few drawbacks that need to be considered. First of all, the synthetic accessibility of both enantiomers of **4**, requires the use of preparative chiral HPLC. This separation has been carried out on a multigram scale, but this cannot routinely be carried out in every laboratory. Furthermore, enolate **5** is highly unstable which requires working at an unusual low temperature and limits derivatisation to aldol condensations with highly reactive aldehydes. This instability is associated with the benzyloxycarbonyl protection, as alkylation of the benzoyl protected analogue of **4** can readily be achieved at -78°C in high yield and excellent diastereoselectivity[15]. This type of protection however, requires acidic hydrolysis as the final step, and thus necessitates ion-exchange chromatography.

From the above it will be clear, that an alternative synthesis of **4**, possibly with a different protecting group and which does not involve a tedious chromatographic resolution procedure, is desirable.

4.3 Baeyer-Villiger oxidation of azetidin-3-ones

Examination of the structure of oxazolidin-5-one **4** reveals that such a compound can, in principle, be obtained by a regio- and stereoselective oxidative ring expansion of 2-substituted azetidin-3-ones (Scheme 2).

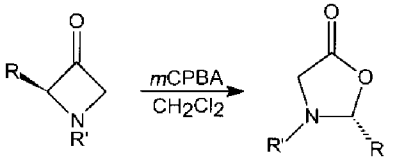
Scheme 2 *Oxidative ring expansion of azetidin-3ones*



Regio- and stereoselective ring expansions of substituted cyclic ketones have been achieved by a Baeyer-Villiger oxidation[16], using either hydrogen peroxide in the presence of base or transition metal salts, or, more commonly, peracids, *e.g.* trifluoroperacetic acid and *meta*-chloroperbenzoic acid (*m*CPBA)[17]. The regioselectivity of this reaction is the result of the higher migratory aptitude of secondary carbon atoms over primary ones. The concerted mechanism of the reaction ensures retention of configuration at the migrating centre. If the Baeyer-Villiger oxidation could be extended to azetidin-3-ones, a range of enantiomerically pure oxazolidin-5-ones comes within reach without the need of a resolution step, as various substituted azetidin-3-ones can readily be prepared from homochiral α-amino acids (see Chapter 2).

The Baeyer-Villiger approach is the subject of this chapter. Preparation of oxazolidin-5-ones by a Baeyer-Villiger oxidation of azetidin-3-ones was investigated with the azetidin-3-ones **7a-g**. These four-membered ring substrates **7** all contain a sterically demanding 2-substituent which is important in view of the use of the oxazolidin-5-one derived thereof, as chiral glycine equivalent. When treated with one equivalent of dry *m*CPBA in dichloromethane at ambient temperature, all azetidin-3-ones **7** underwent a smooth reaction, resulting in the formation of the desired oxazolidin-5-ones as the only product in acceptable to good yields (Table 1).

Table 1 *Baeyer-Villiger oxidation of some azetidin-3-ones* **7** *to 1,3-oxazolidin-5-ones*



7 **8**

7	R	R′	cy[a] **8** (%)
a	*i*Pr	Cbz	82
b	*t*Bu	Cbz	57
c	Bn	Ts	60
d	*i*Pr	Ts	59
e	*i*Bu	Ts	52
f	*s*Bu	Ts	76
g	*t*Bu	Ts	76

[a] isolated yield after column chromatography and crystallisation

The analytical data, including the optical rotation, of oxazolidin-3-one **8b**, which was derived from Cbz-*tert*Leu , were in full agreement with those previously reported[14] . This indicates that the reaction proceeds with complete regio- and stereoselectivity. However, the optical rotation is rather small and the literature is not fully unambiguous about this[14]. Therefore, an alternative proof for the absence of racemisation was needed. For this purpose the oxazolidin-5-one **8d** and its antipode derived from D-Val were prepared. HPLC analysis of these two compounds showed both of them were more than 98% optically pure, indicating less than 1% racemisation over the four reaction steps. This observation unambiguously proves the stereoselectivity of the Baeyer-Villiger oxidation and confirms that this approach is an excellent alternative for the preparation of enantiopure oxazolidin-5-ones.

4.4 Attempted synthesis of α-amino acids from 1,3-oxazolidin-5-ones

The procedure for the use of 1,3-oxazolidin-5-ones as chiral glycine equivalent involves an initial deprotonation followed by a reaction with a suitable electrophile, *e.g.* an alkyl halide or an aldehyde. The tosyl protected substrates **8d** and **8g** were investigated first (Table 2).

Table 2 *Results of attempted derivatisation of* **8d** *and* **8g**

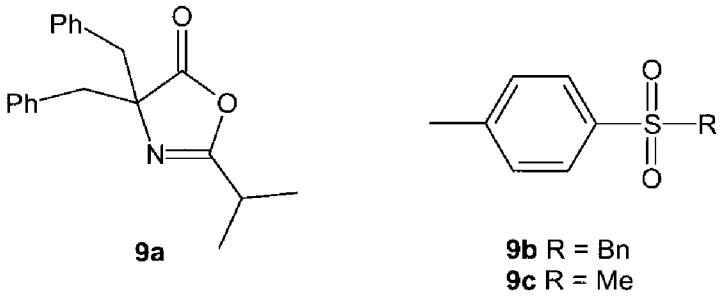
oxazolidin-5-one	base	electrophile	result
8d	iPr$_2$NLi	PHCHO	decomp.
8d	iPr$_2$NLi	BnBr	decomp.
8d	iPr$_2$NLi	MeI	decomp.
8g	(Me$_3$Si)$_2$NLi[a]	PhCHO	decomp.
8d	iPr$_2$NLi[b]	BnBr	35% **7a**, 28% **7b**
8d	iPr$_2$NLi[b]	MeI	71% **7c**
8d	iPr$_2$NLi	NH$_4$Cl	decomp.
8d	(Me$_3$Si)$_2$NLi	NH$_4$Cl	decomp.
8d	(Me$_3$Si)$_2$NLi	D$_2$O	decomp.

[a] -100 °C; [b] 20 vol% HMPA

Deprotonation of **8d** with LDA at -78 °C and subsequent addition of benzaldehyde, benzyl bromide or methyl iodide led to complete decomposition of the starting material. Benzaldehyde could be recovered unchanged. The use of lithium hexamethyldisilazane, previously found to be the best base[14], and an even lower reaction temperature (-100 °C), gave the same result for **8g**. Remarkably, the decomposition does not take place until the bath temperature has reached approximately -20 °C, as could be judged from the instantaneous blackening of the

reaction mixture at this temperature. Apparently, the enolate is reasonably stable at low temperature but insufficiently reactive. To enhance the enolate reactivity the polar aprotic co-solvent hexamethylphosphoramide (HMPA) was added. Now, a reaction *does* occur with benzyl bromide and methyl iodide even at low temperature, although the mixture still turns black. The products **9a-c** (Figure 2) were isolated instead of the expected alkylated oxazolidin-5-ones.

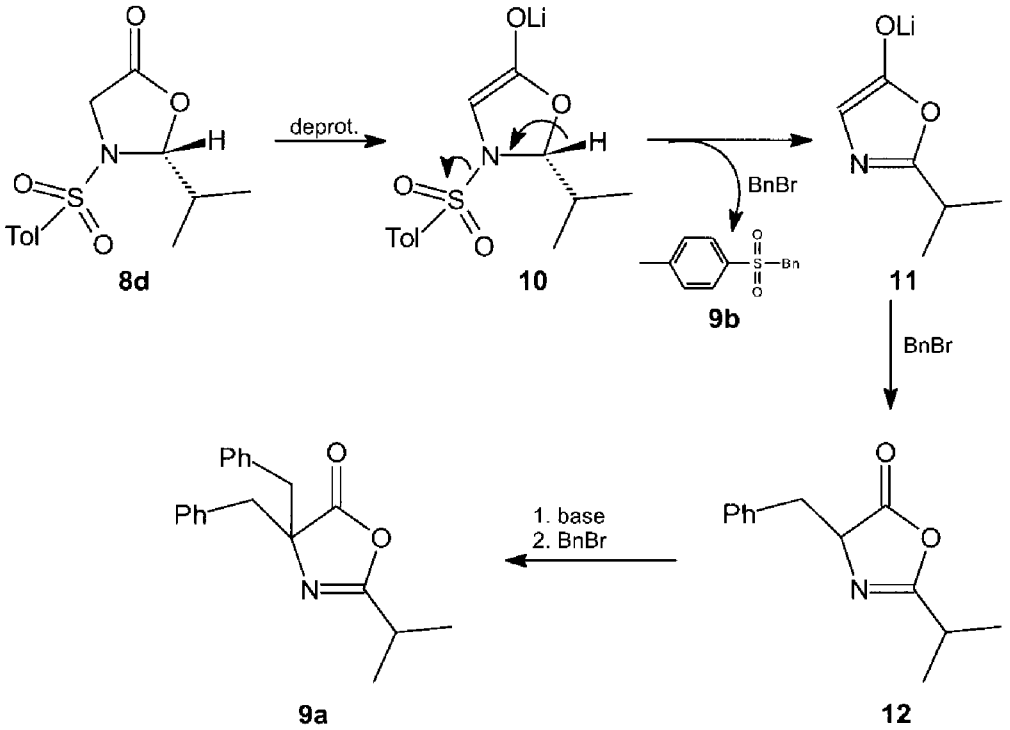
Figure 2 *Reaction products of the reaction of* **8d** *with benzylbromide and methyliodide in the presence of HMPA*



9a **9b** R = Bn
9c R = Me

The formation of these deviant products is tentatively explained as depicted in scheme 3.

Scheme 3 *Tentative mechanism to explain the formation of* **9a** *and* **9b**



Apparently, an elimination of p-toluenesulphinate takes place, after which a double deprotonation and subsequent alkylation sequence leads to the isolated product **9a**.

The eliminated sulphinate is trapped by benzyl bromide which gives rise to **9b**. The intermediate **10** could not be isolated after quenching with D_2O.

Next the benzyloxycarbonyl protected substrates **8a** and **8b** were considered. The *tert*-butyl substituted compound **8b** has been used successfully by Seebach *et al.*[15] who performed an aldol condensation with a variety of aldehydes. The substrate **8a** with an *iso*-propyl substituent is easier to obtain as it can be prepared from inexpensive material, namely the amino acid valine. The results of attempted reactions with substrates **8a** and **8b** are collected in Table 3.

Table 3 *Attempted derivatisation of* **8a** *and* **8b**

oxazolidin-5-one	base	electrophile	result
8a	$(Me_3Si)_2NLi$	BnBr	decomp.
8a	$(Me_3Si)_2NLi$	BnI	decomp.
8a	$(Me_3Si)_2NLi$	BnI	decomp.
8a	$(Me_3Si)_2NLi$	MeI	decomp.
8a	$(Me_3Si)_2NLi$	MeI[b]	decomp.
8a	$(Me_3Si)_2NLi$	MeI	decomp.
8a	$(Me_3Si)_2NLi$	PhCHO	decomp.
8a	$(Me_3Si)_2NLi$	PhCHO[c]	decomp.
8b	$(Me_3Si)_2NLi$	PhCHO	aldol aduct 69%

[a] 20 vol% HMPA; [b] 5 equiv.; [c] reverse order of addition

Disappointingly, in all cases decomposition took place even at -100 °C. Addition of HMPA did not alter this situation. Remarkably, the *tert*-butyl containing substrate **8b** did react smoothly with benzaldehyde after deprotonation using lithium hexamethyldisilazane at -100 °C. This difference in behaviour between **8a** (*i*Pr) and **8b** (*t*Bu) was entirely unexpected. Apparently, steric stabilisation plays an important role.

As an alternative it was attempted to isolate the enolates as their silyl ethers. Thus, after base treatment, the reaction mixture was treated with silylating agents as shown in Table 4. However, in all cases decomposition was observed, even in the presence of the co-solvent HMPA.

Table 4 *Attempted conversion of* **8a** *and* **8d** *into silyl enol ethers*

oxazolidin-5-one	silylating agent	base	result
8d	Me_3SiCl	$(Me_3Si)_2NLi$[a]	decomp.
8d	$tBuPh_2siCl$	$(Me_3Si)_2NLi$[a]	decomp.
8d	$Me_2PhSiCl$	$(Me_3Si)_2NLi$[a]	decomp.
8a	$tBuMe_2SiCl$	iPr_2NLi	decomp.
8a	$tBuMe_2SiCl$	$(Me_3Si)_2NLi$	decomp.
8a	$tBuPh_2siCl$	$(Me_3Si)_2NLi$[a]	decomp.
8a	$Me_2PhSiCl$	$(Me_3Si)_2NLi$[a]	decomp.

[a] 20 vol% HMPA

The conclusion of these deprotonation/alkylation studies is that only the *tert*-butyl substituted oxazolidin-5-one **8b** is suitable as chiral glycine equivalent. Other substituents than *tert*-butyl at the oxazolidin-5-one lead to uncontrolled decomposition.

4.5 Concluding remarks

An alternative synthesis of homochiral 1,3-oxazolidin-5-ones based on the Baeyer-Villiger oxidation of 2-substituted azetidin-3-ones has been developed. This approach enables the preparation of a range of various substituted oxazolidin-5-ones, without the need of a tedious resolution procedure.

Application of the prepared oxazolidin-5-ones as chiral glycine α-anion equivalent in the asymmetric synthesis of α-amino acids failed due to the instability of the corresponding enolates, except for the *tert*-butyl substituted derivative **8b**. Apparently, the nature of the substituent at C-2 of the oxazolidin-5-ones is of critical importance for their successful use as chiral glycine equivalent.

4.6 Experimental Part

General remarks

Melting points were determined using a Reichert thermopan microscope and are uncorrected. Optical rotations were measured with a Perkin Elmer automatic polarimeter, model 241 MC, using concentrations *c* in g/100 ml at 20 °C in the solvents indicated. ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AC 100 (100 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer. The chemical shift δ is given in ppm relative to the internal standard (TMS for ^{1}H-NMR, $CDCl_3$ for ^{13}C-NMR). IR spectra were recorded on a Perkin Elmer 298 spectrophotometer. The wavenumber ν is listed in cm^{-1}. For (high resolution) mass spectra a double focussing VG7070E mass spectrometer was used. GC-MS were measured using a Varian Saturn II GC-MS by on-column injection (DB-1 column, length 30

m, internal diameter 0.25 mm, film thickness 0.25 μm). Elemental analyses were performed using a Carlo Erba Instruments CHNS-O EA 1108 element analyzer.HPLC analysis of **8d** and its antipode was carried out using a Chiralcel OD-H column and hexane-ethanol (95/5 , 1 ml/min) as the eluent.

Chemicals
THF was pre-distilled from calcium hydride, and prior to use distilled from sodium/benzophenone. Hexane, ethyl acetate and dichloromethane were distilled from calcium hydride and stored over 4 Å molsieves. *m*CPBA was dried by dissolution in CH_2Cl_2, separation of the layers, subsequent drying over $MgSO_4$ and concentration *in vacuo*. All other reagents were analytic grade and used as such.

General procedure (GP1) for the preparation of the oxazolidin-5-ones **8a-8g**
To a solution of the azetidin-3-one in dry CH_2Cl_2 (~ 0.5M) was added 1.1 equiv. of dried *m*CPBA. The reaction mixture was stirred at ambient temperature until TLC-analysis showed completion of the reaction. Then, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution. The water layer was extracted three times with CH_2Cl_2 after which the combined organic layers where washed with brine (3x), dried with Na_2SO_4 and concentrated *in vacuo*. The oxazolidinone obtained was purified by flash column chromatography followed by crystallisation from di*iso*propyl ether/hexane.

(S)-2-*iso*Propyl-3-benzyloxycarbonyl-1,3-oxazolidin-5-one **8a**

7a 1.5 g (6.1 mmol) was treated according to GP1 to give, after column chromatography (hexane:ethyl acetate 4:1 (v/v)) and crystallisation, 1.31 g (57%) **8b** as a white crystalline material, mp 60 °C, $[a]_D^{20}$ +19.8 ° (*c* = 1, $CHCl_3$).^{1}H NMR (100 MHz) δ : 0.96 (2xd, *J* = 6.8 Hz, 6H, $CH(CH_3)_2$), 2.20 (m, 1H, $CH(CH_3)_2$), 4.09 (dd, J_{AB} = 17.4 Hz, 2H, NCH_2CO), 5.18 (s, 2H, CH_2Ph), 5.71 (d, *J* = 3.4 Hz, C*H*iPr), 7.36 (m, 5H, arom.). ^{13}C NMR (25 MHz, $CDCl_3$) δ : 14.4 ($CH(CH_3)_2$), 16.9 ($CH(CH_3)_2$), 33.1 ($CH(CH_3)_2$), 45.4 (CH_2Ph), 87.9 (NCH_2), 94.0 (C*H*iPr), 128.5 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 135.4 (C_{Ar}), 153.2 (N*C*=O), 169.7 (*C*=O). IR ($CHCl_3$) ν : 3000-2800, 1800, 1700. $C_{14}H_{17}NO_4$ (263.29) C 63.87 H 6.51 N 5.32 found C 64.11 H 5.95 N 5.31.

(S)-2-*tert*-Butyl-3-benzyloxycarbonyl-1,3-oxazolidin-5-one **8b**

7b 0.5 g (1.9 mmol) was treated according to GP1 to give, after column chromatography (hexane:ethyl acetate 6:1 (v/v)) and crystallisation, 0.3 g (57%) **8b** as a white crystalline material, mp 60-61°C [lit], $[a]_D^{20}$ -5.1 ° (*c* = 1, $CHCl_3$). [lit.[14] -4.0 ° (*c* = 1, $CHCl_3$)]. ^{1}H NMR (100 MHz) δ : 0.94 (s, 9H, *t*Bu), 4.06 (dd, J_{AB} = 17.6 Hz, 2H, NCH_2CO), 5.26 (s, 2H, CH_2Ph), 5.62 (s, 1H, C*H*tBu), 7.55 (m, 5H, C_6H_5). ^{13}C NMR (25 MHz) d : 21.5 ($CH_3C_6H_4$), 24.3 ($C(CH_3)_3$), 37.9 ($C(CH_3)_3$) 47.4 (NCH_2CO), 98.5 (C*H*tBu), 127.7 ($C_{Ar}H$), 130.4 ($C_{Ar}H$), 132.5 (C_{Ar}), 145.5 ($C_{Ar}H$), 169.7 (C=O).IR ($CHCl_3$) ν : 3000-2800, 1800, 1700. MS *m/z* (%) : 234 (12) [M^+ + 1 - CO_2], 98 (5) [M^+ - CO_2 - Z], 91 (100). $C_{15}H_{19}NO_4$ (277.13) calc. C 64.97 H 6.91 N 5.05 found C 65.21 H 6.76 N 5.10.

(S)-2-Benzyl-3-tosyl-1,3-oxazolidin-5-one **8c**

7c 1.75 g (5.5 mmol) was treated according to GP1 to give, after column chromatography (hexane:ethyl acetate 4:1 (v/v)) and crystallisation 1.10 g (60%) **8c** as a white crystalline material, mp 125-126 °C, $[a]_D^{20}$ -77.1 ° (*c* = 1, $CHCl_3$). ^1H NMR (100 MHz) d : 2.44 (s, 3H, $CH_3C_6H_4$), 3.20 (s, 2H, CH_2Ph), 3.39 (dd, ^2J = 17.6 Hz, 2H, NCH_2CO), 5.96 (t, ^3J = 3.7 Hz, 1H, *CH*Bzl), 7.30 (m, 7H, C_6H_5 and $C_6H_4CH_3$), 7.70 (d, *J* = 8.2 Hz, 2H, $C_6H_4CH_3$). ^{13}C NMR (25 MHz) d : 21.6 ($CH_3C_6H_4$), 36.6 (CH_2Ph), 69.9 (NCH_2CO), 85.2 (*C*HBzl), 127.0 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 130.0 ($C_{Ar}H$), 131.6 (C_{Ar}), 134.9 (C_{Ar}), 145.0 (C_{Ar}), 196.0 (*C*=O). IR ($CHCl_3$) ν (cm^{-1}): 1800 (C=O), 1595, 1360, 1155. $C_{17}H_{17}NO_4S$ (331.38) calcd. C 61.62 H 5.17 N 4.23 found C 61.03 H 4.67 N 4.30

(S)-2-*iso*Propyl-3-tosyl-1,3-oxazolidin-5-one **8d**

7d 0.27 g (1.0 mmol) was treated according to GP1 to give, after column chromatography (hexane:ethyl acetate 8:1 (v/v)) and crystallisation 0.17 g (59%) **8d** as a white crystalline material, mp 85 °C, $[a]_D^{20}$ -24.1° (*c* = 1, $CHCl_3$). ^1H NMR (100 MHz) d : 1.03 (dd, ^3J = 4.5 Hz, 6H, $(CH_3)_2CH$), 2.04 (m, 1H, $CH(CH_3)_2$), 2.45 (s, 3H, $CH_3C_6H_4$), 3.94 (dd, ^2J = 17.9 Hz, 2H, NCH_2CO), 5.74 (d, ^3J = 5.5 Hz, 1H, *CH*iPr), 7.38 (d, *J* = 8.3 Hz, 2H, $C_6H_4CH_3$), 7.72 (d, *J* = 8.2 Hz, 2H, $C_6H_4CH_3$). ^{13}C NMR (25 MHz) d : 16.0 ($CH(CH_3)_2$), 17.3 ($CH_3C_6H_4$), 21.7 ($CH(CH_3)_2$), 46.6 (NCH_2CO), 96.3 (*C*HiPr), 127.6 ($C_{Ar}H$), 130.6 ($C_{Ar}H$), 132.8 (C_{Ar}), 145.6 (C_{Ar}), 169.5 (*C*=O). IR ($CHCl_3$) n (cm^{-1}): 1800 (C=O), 1595, 1355, 1150. MS *m/z* (%): 283 (2) [M^+], 240 (6) [M^++1-CO_2], 155 (4) [$C_7H_7SO_2^+$], 91 (15) [$C_7H_7^+$], 43 (100) [$C_3H_7^+$]. $C_{13}H_{17}NO_4S$ (283.34) calcd. C 55.11 H 6.05 N 4.94 found C 54.96 H 5.92 N 5.02.

(S)-2-*iso*Butyl-3-tosyl-1,3-oxazolidin-5-one **8e**

7e 0.71 g (2.5 mmol) was treated according to GP1 to give, after column chromatography (hexane:ethyl acetate 8:1 (v/v)) and crystallisation 0.38 g (52%) **8e** as a white crystalline material, mp 89 °C, $[a]_D^{20}$ -10.5° (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz) d : 1.00 (dd, ^3J = 1.1 Hz, 6H, $(CH_3)_2CH$), 1.70 (m, 2H, CH_2iPr), 1.87 (m, 1H, $CH(CH_3)_2$), 2.46 (s, 3H, $CH_3C_6H_4$), 3.95 (dd, ^2J = 17.9 Hz, 2H, NCH_2CO), 5.76 (t, ^3J = 6.5 Hz, 1H, *CH*iBu), 7.38 (d, *J* = 8.2 Hz, 2H, $C_6H_4CH_3$), 7.71 (d, *J* = 8.2 Hz, 2H, $C_6H_4CH_3$). ^{13}C NMR (100 MHz) d : 21.6 ($CH_3C_6H_4$), 22.2 and 22.5 ($CH(CH_3)_2$), 24.0 ($CH(CH_3)_2$), 44.8 (CH_2iPr), 45.7 (NCH_2CO), 91.5 (*C*HiBu), 127.8 ($C_{Ar}H$), 130.5 ($C_{Ar}H$), 136.3 (C_{Ar}), 145.5 (C_{Ar}), 169.1 (C=O). IR ($CHCl_3$) n (cm^{-1}): 1800 (C=O), 1600, 1365, 1160. MS *m/z* (%): 297 (8) [M^+], 240 (49) [M^+- $C_4H_9^+$], 155 (86) [$C_7H_7SO_2$+], 91 (20) [$C_7H_7^+$], 41 (100). $C_{14}H_{19}NO_4S$ (297.10) calcd. C 56.55 H 6.44 N 4.71 found C 55.93 H 6.60 N 4.69.

(S)-2-*sec*-Butyl-2-tosyl-1,3-oxazolidin-5-one **8f**

7f 0.99 g (3.5 mmol) was treated according to GP1 to give, after column chromatography (hexane:ethyl acetate 8:1 (v/v)) and crystallisation 0.79 g (76%) **8f** as a white crystalline material, mp 106 °C, $[a]_D^{20}$ -7.8° (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz) d : 1.00 (m, 6H, 2xCH_3), 1.25 (m, 1H, $CH(H)CH_3$), 1.61 (m, 1H, $CH(H)CH_3$), 1.84 (m, 1H, *CH*(Me)Et), 2.46 (s, 3H, $CH_3C_6H_4$), 3.96 (dd, ^2J = 17.9 Hz, 2H, NCH_2CO), 5.54 (d, ^3J = 5.1 Hz, CH_2sBu), 7.38 (d, *J* = 8.0 Hz, 2H, $C_6H_4CH_3$), 7.72 (d, *J* = 8.0 Hz, 2H, $C_6H_4CH_3$). ^{13}C NMR (100 MHz) d : 11.1 (CH_3CH_2), 12.2 (CH_3CH), 21.5 ($CH_3C_6H_4$), 24.2 (CH_2CH_3), 40.8 (CH(Me)Et), 46.4 (NCH_2CO), 95.2

(CHsBu), 127.6 ($C_{Ar}H$), 130.4 ($C_{Ar}H$), 136.0 (C_{Ar}), 145.5 (C_{Ar}), 169.4 (C=O). IR ($CHCl_3$) n (cm^{-1}): 1795 (C=O), 1595, 1360, 1155. MS *m/z* (%): 281 (23) [M^+ - O], 207 (45) [M^+ +1-C_7H_7], 91 (12) [$C_7H_7^+$], 57 (53) [$C_4H_9^+$], 43 (100). $C_{14}H_{19}NO_4S$ (297.10) calcd. C 56.55 H 6.44 N 4.71 found 56.31 H 6.34 N 4.72.

(S)-2-*tert*-Butyl-3-tosyl-1,3-oxazolidin-5-one **8g**

7g 2.5 g (8.9 mmol) was treated according to GP1 to give, after column chromatography (hexane:ethyl acetate 9:1 (v/v)) and crystallisation 2.0 g (76%) **8g** as a white crystalline material, mp 95-96 °C, $[a]_D^{20}$ -18.1 ° (*c* = 1, $CHCl_3$). ^1H NMR (100 MHz) d : 1.02 (s, 9H, *t*Bu), 2.45 (s, 3H, $CH_3C_6H_4$), 3.93 (dd, J_{AB} = 18.4 Hz, 2H, NCH_2CO), 5.43 (s, 1H, CHtBu), 7.37 (d, *J* = 8.1 Hz, 2H, $C_6H_4CH_3$), 7.73 (d, *J* = 8.1 Hz, 2H, $C_6H_4CH_3$). IR ($CHCl_3$) ν : 1790 (C=O), 1595, 1360 (SO_2) ^{13}C NMR (25 MHz) δ : 21.5 ($CH_3C_6H_4$), 24.3 ($C(CH_3)_3$), 37.9 ($C(CH_3)_3$) 47.4 (NCH_2CO), 98.5 (CHtBu), 127.7 ($C_{Ar}H$), 130.4 ($C_{Ar}H$), 132.5 (C_{Ar}), 145.5 ($C_{Ar}H$), 169.7 (*C*=O). MS *m/z* (%): 298 (35) [M^+ + 1], 155 (15) [Ts], 98 (100) [M^+ - Ts - CO_2].$C_{14}H_{19}NO_4S$ (297.10) Calc. C 56.55 H 6.44 N 4.71 found C 56.71 H 6.46 N 4.82.

Deprotonation experiments

*General procedure 2 (GP2) (oxazolidinones **8d** and **8g**) :*

To a cooled (-78 °C) solution of base (LHMDS or LDA, 1 equiv.) in THF (1 ml) a pre-cooled solution of oxazolidinone (0.3 mmol) in THF (1 ml) was added dropwise *via* a syringe. The light yellow solution was stirred at this temperature for 20 min, after which 400 µl of HMPA (were appropriate) and a solution of the electrophile (1.2 equiv.) in THF (1 ml) was added. The now colourless solution was allowed to reach ambient temperature and was subsequently quenched with a saturated aqueous NH_4Cl solution. The organic layer was washed with a saturated aqueous NH_4Cl solution (2 x 5 ml) after which the combined aqueous layers were extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*.

*General procedure 3 (GP3) (oxazolidinones **8a** and **8b**) :*

To a cooled solution of oxazolidinone (4 mmol) in THF (50 ml) a cooled (-78 °C) solution of LHMDS (1 equiv.) in THF (1 ml) was added *via* a cannula. The light yellow solution was stirred for 15-20 minutes and then cooled to -100 °C (liq. N_2/Et_2O). A solution of aldehyde (1.1 equiv) in THF (5 ml) was then added using a syringe and the resulting solution stirred for another 15-20 minutes, during which the temperature was not allowed to exceed -100 °C. The reaction was quenched by the addition of AcOH (1N, 8.8 ml) in THF. After 2 min, the mixture was poured into a mixture of a saturated aqueous NH_4Cl-solution (50 ml) and Et_2O (50 ml). The water layer was extracted with Et_2O (50 ml) after which the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*.

General procedure 4 (GP4) (silylation experiments).

A solution of oxazolidinone (0.3 mmol), HMPA (0.2 equiv.) and R_3SiCl (1.1. equiv.) in THF (1 ml) was cooled to -65 °C. A pre-cooled solution base (LHMDS or LDA, 1 equiv.) in THF (1ml) was added using a syringe and the resulting yellow suspension stirred for 20 min. The reaction was quenched by the addition of water (5 ml) and diluted with 5 ml Et_2O. The water layer was extracted with Et_2O (3 x 5 ml) and the combined organic layers washed with a saturated aqueous NaCl-solution, dried over Na_2SO_4 and concentrated *in vacuo*.

Oxazolidin-5-one **8d** (0.40 g, 1.4 mmol) was treated according to GP2 (benzyl bromide) , to give after column chromatography (hexane : ethyl acetate 5:1 v/v)) 0.15 g **9a** (35%) and 0.98 **9b** (28%) as white solids.

4,4-Dibenzyl-2-*iso*propyl-4H-oxazol-5-one **9a** : ^{1}H NMR (100 MHz, $CDCl_3$) : δ 0.75 (d, ^3J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.25 (m, 1H, $CH(CH_3)_2$), 3.21 (s, 4H, CH_2Ph), 7.20 (m, 10H, arom.). ^{13}C (25 MHz, $CDCl_3$) : δ 18.1 ($CH(CH_3)_2$), 26.5 ($CH(CH_3)_2$), 43.3 (CH_2Ph), 74.9 (CBn_2), 127.2 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 130.2 ($C_{Ar}H$), 134.5 (C_{Ar}), 167.6 N=*C*), 179.6 (*C*=O). IR ($CHCl_3$) : ν (cm^{-1}) 1800 (C=O), 1670 (C=N). MS (EI) *m/z* (%) : 306 (21) [M^+-1], 237 (2), 220 (18), 91 (100).

Benzyl tolyl sulphone **9b** : ^{1}H NMR (100 MHz, $CDCl_3$) : δ 2.32 (s, 3H, CH_3), 4.20 (s, 2H, CH_2Ph), 6.98-7.45 (m, 9H, arom.). IR ($CHCl_3$) : ν (cm^{-1}) 1315, 1150. MS (EI) *m/z* (%) : 246 (3) [M^+], 182 (7), 139 (6), 91 (100).

Oxazolidin-5-one **8d** (0.21 g, 0.7 mmol) was treated according to GP2 (methyl iodide) , to give after column chromatography (hexane : ethyl acetate 5:1 v/v) 8 mg **9c** (67%) as a white solid.

Methyl tolyl sulphone **9c** : ^{1}H NMR (100 MHz, $CDCl_3$) : δ 2.37 (s, 3H, $CH_3C_6H_4$), 2.96 (s, 3H, CH_3SO_2), 7.25 (d, 2H, J = 8.2 Hz, C_6H_4), 7.72 (d, 2H, J = 8.2 Hz, C_6H_4).

4.7 References

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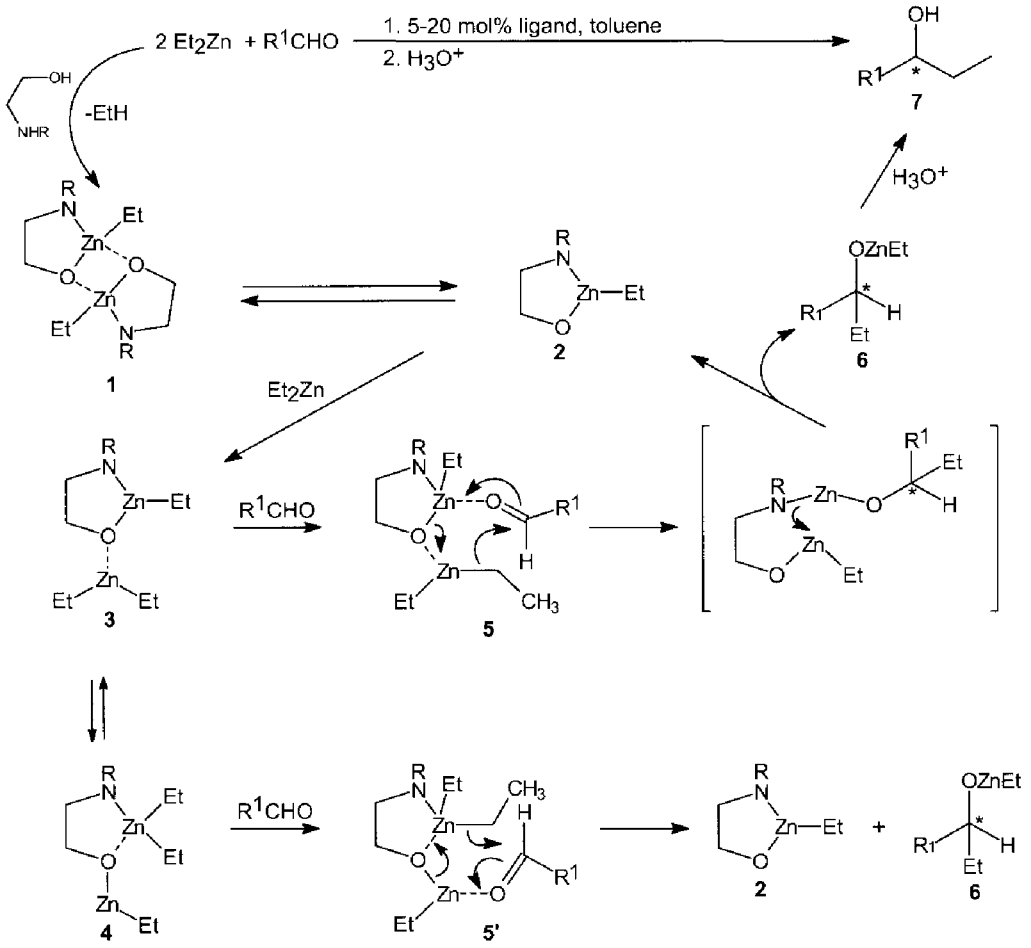
5 Enantioselective diethylzinc addition to aldehydes using azetidine derived amino alcohols

5.1 Introduction

The nucleophilic addition of organometallic reagents to aldehydes, catalysed by appropriate chiral ligands is one of the most extensively studied methods for the asymmetric carbon-carbon formation[1]. The reaction of aromatic aldehydes with diethylzinc catalysed by various chiral β- and γ-amino alcohols has been particularly successful, to give 1-aryl-1-ethanols in both excellent chemical and optical yield[2].

Scheme 1 *Catalytic cycle of the reaction of aldehydes with diethylzinc*



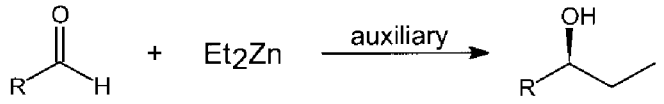
Due to the poor polarisation of the carbon-zinc bond, monomeric dialkylzinc reagents are inherently unreactive towards aldehydes[3] and hence activation by the amino alcohol is essential in order to obtain an appreciable nucleophilic addition. Mechanistically, this process is well understood[3-6] (Scheme 1). The initial step towards this activation is the formation of zinc alkoxide **2**, which is the actual catalytic species[4]. Co-ordination of a second molecule of diethylzinc to **2** generates the mono-alkoxide zinc complexes **3** and **4**[6]. The dialkylzinc moiety in these complexes is activated due to the co-ordination with the electronegative heteroatoms, which increases the polarity of the alkyl-zinc bond and consequently enhances the nucleophilicity of the alkyl groups[3]. Both metal centres are essentially tetrahedral[7] and the co-ordinatively unsaturated zinc atom therefore forms an excellent docking point for the aldehyde, its acceptor character being enhanced by the co-ordination to the electronegative oxygen atom[3,8]. This results in the formation of complexes **5** and **5'**, in which the actual nucleophilic addition takes place, probably *via* a cyclic 6-membered ring transition state, under the formation of zinc alkoxide **6** and the regeneration of catalyst **2**. It is important to note that alkylzinc compounds are generally fluxional in nature and undergo ready interconversion with possible structural isomers by intra- and intermolecular processes[3]. This means that alternative pathways, encompassing structures not shown in scheme 1, can and probably do take place. Extensive studies however, have demonstrated that the intermediates depicted in scheme 1 are the most significant ones[3,4], making this mechanism generally accepted.

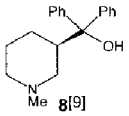
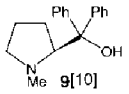
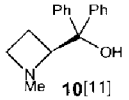
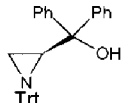
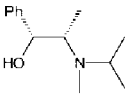
The lack of reactivity of diethylzinc in the absence of amino alcohols makes this reaction ideal to be carried out in a catalytic fashion, under easily controllable conditions. This is in contrast to many other organometallic reagents, which generally require stoichiometric amounts of ligand in combination with very low reaction temperatures for an effective stereocontrolled addition reaction. As a result, this method using diethylzinc has been employed frequently with a variety of amino alcohols, producing secondary alcohols in both excellent chemical and optical yield.

5.2 Heterocyclic amino alcohols as chiral auxiliary

The enantioselective addition of diethylzinc to both aromatic and aliphatic aldehydes, catalysed by chiral amino alcohols, including various derivatives of cyclic amines, has been studied extensively. A selection of some representative examples is collected in Table 1.

Table 1 *Enantioselectivity of the diethylzinc addition to aldehydes, catalysed by amino alcohols.*



auxiliary	R (*ee* %)				
	Ph	*p*-MeOPh	*n*-pentyl	*n*-hexyl	*n*-octyl
 **8**[9]	74	70	45	--	--
 **9**[10]	97	81	--	91	--
 **10**[11]	98	100	--	--	68
 **11**[18]	99	99	--	80	--
 **12**[20,21]	80	--	--	79	--

The data in this table clearly reveal that the enantioselectivity of the reaction appears to be susceptible to changes of the size of ring of the auxiliary. Usually a smaller ring size leads to more effective auxiliaries, with amino alcohols **10** and **11** as the best ones. This positive behaviour of the three and four-membered ring catalysts can probably be attributed to their rather rigid cyclic backbone. Furthermore, the inducing capability of all these auxilaries is acceptable to excellent in the case of *aromatic* aldehydes, however, their effectiveness is considerably lower when applied to *aliphatic* aldehydes. This difference in behaviour of aromatic and aliphatic aldehydes is characteristic for most β-amino alcohols[12] implying that there is still a need for new auxiliaries for this diethylzinc reaction, especially amino alcohols which are also successful in the asymmetric addition to aliphatic aldehydes.

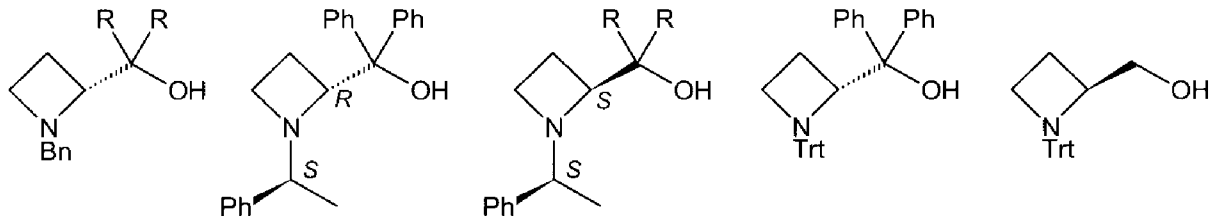
These two facts make this particular asymmetric process an ideal reaction to study the effectiveness of functionalised azetidines as chiral auxiliary, especially as compared to their, much more frequently used, five-membered ring analogues. For this reason the effectiveness of amino alcohols derived from functionalised azetidines was further explored to uncover their potential as chiral auxiliary in diethylzinc

addition reactions to aromatic *and* aliphatic aldehydes. The results of this study are described in this chapter.

5.3 Synthesis of azetidine derived auxiliaries

The disappointing result obtained with azetidine **10** in the case of the aliphatic aldehyde nonanal[10], shows that a rigid cyclic backbone is not sufficient for a chiral auxiliary to be effective. However, from analogues work using aziridine derived amino alcohols, it became clear that fine-tuning of the auxiliary by introducing (subtle) structural changes in the molecule, can have a profound effect on the efficiency of the auxiliary with regard to the enantioselectivity of the reaction[13,18a]. These heterocyclic amino alcohols offer two positions for structural alteration *viz.*, the alcohol moiety and the nitrogen substituent. The azetidines **13-19** (Figure 1), were used in the study described in this chapter.

Figure 1 *Azetidine derived β-amino alcohols used in the diethylzinc addition reaction*



13 R = Ph
14 R = H

15

16 R = H
17 R = Ph

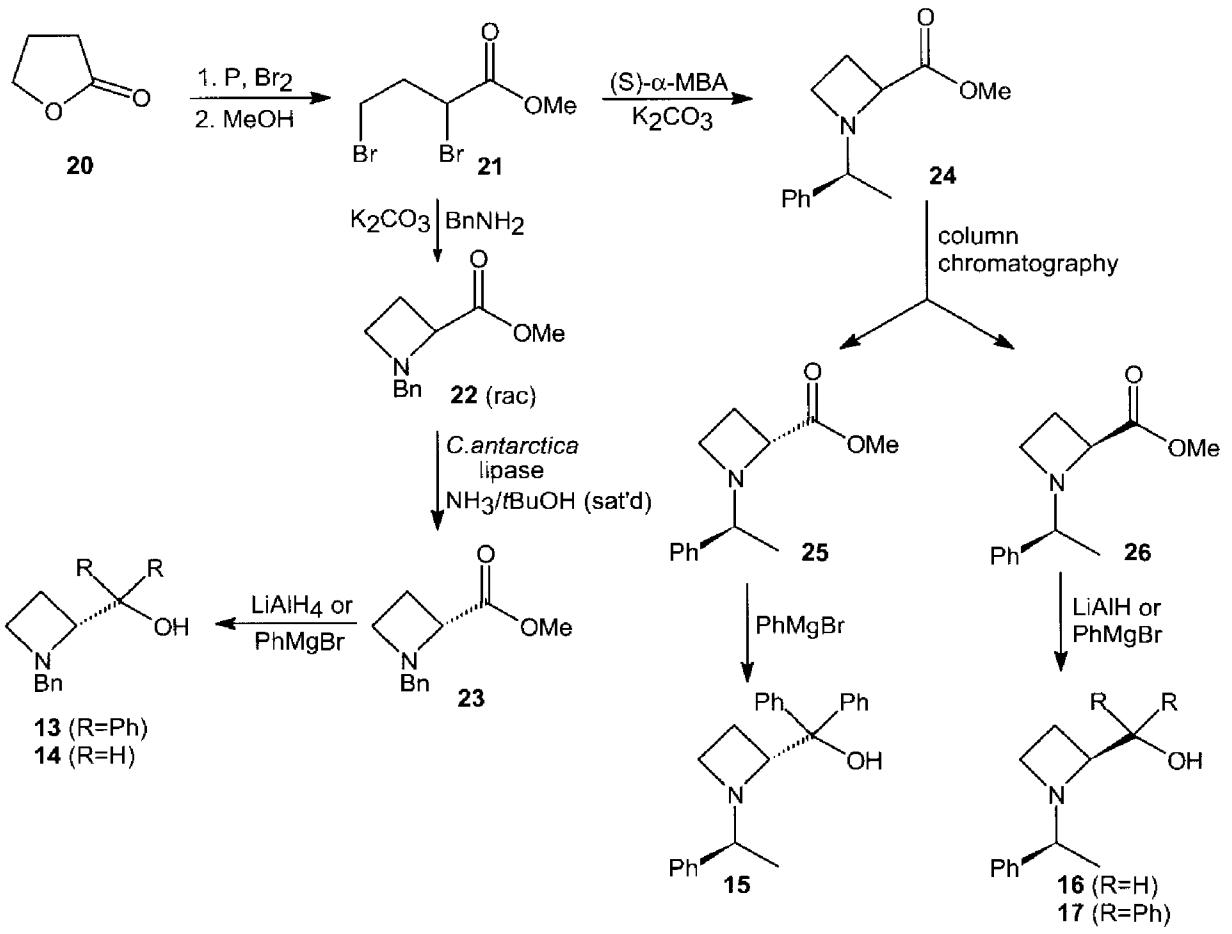
18

19

The potential catalysts **13-17** are readily available in high yields on a multigram scale, as outlined in scheme 2. Reaction of γ–butyrolactone with bromine leads to 2,4-dibromobutanoate **21**. Ringclosure of this dibromide **21** with benzylamine under basic conditions, gives methyl *N*-benzyl-azetidine-2-carboxylate **22** as a racemate in approximately 41% yield. Ammoniolysis using *Candida antarctica* lipase in ammonia saturated *tert*-butyl alcohol, selectively converts the (S)-enantiomer into the corresponding amide, from which the remaining (R)-ester **23** can easily be separated[14]. Similarly, treatment of **21** with optically pure (*S*)-α-methylbenzyl amine and subsequent chromatographic separation of the diastereoisomeric esters, gives the desired (S,R) and (S,S) methyl *N*-methylbenzyl azetidine-2-carboxylates **25** and **26** in an enantiopure form[15]. Treatment of these three esters with the appropriate Grignard reagent or lithiumaluminium hydride gives the amino alcohols **13-17**. Reductive removal of the N-substituent of **15** followed by tritylation gives azetidine **18**. Similarly, amino alcohol **19** was prepared from **14**. It should be noted that the

amino alcohol **10** having a N-methyl substituent is more difficult to prepare, because of the limited availability and high price of the starting material, optically pure azetidine-2-carboxylic acid. Furthermore, only the (*S*) acid is commercially available, its antipode is not.

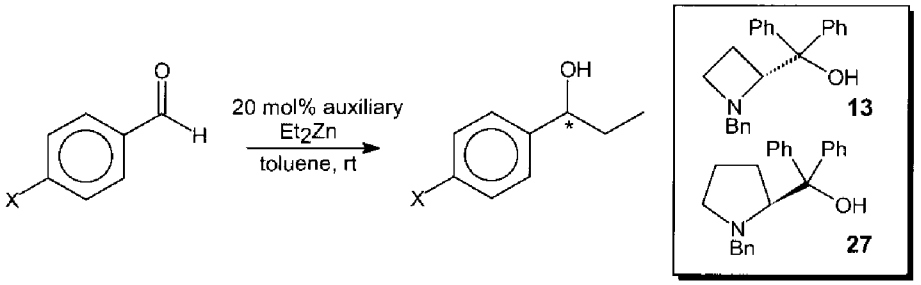
Scheme 2 *Synthesis of the amino alcohols* **13-17**



5.4 Results and Discussion

The azetidine carbinol **13** was tested as chiral auxiliary in the addition of diethylzinc to aromatic aldehydes. The results of this are collected in Table 2. The enantioselectivities achieved for its five-membered ring analogue **27**, which were reported in the literature[16], are also listed in Table 2.

Table 2 *Enantioselective addition of diethylzinc to aromatic aldehydes, catalysed by* **13** *and* **27**



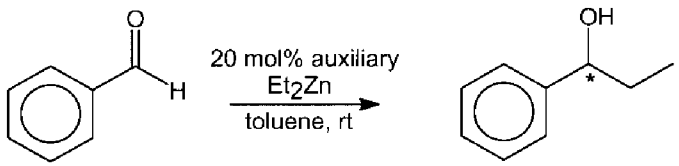
X	Auxiliary	Yield (%)	*ee* (%)[a]	config[b]
H	**13**	62	88	R
H	**27**[c]	92	72[16]	S
H	**27**	n.d[e].	22	S
OMe	**13**	91	>99	R
OMe	**27**[d]	94	79[16]	S
Cl	**13**	80	96	R
Me	**13**	85	95	R

[a] determined by chiral capillary GC using BetaDEX™ by Supelco. [b] based on optical rotation. [c] 10 mol%. [d] 10 mol%, hexane. [e] not determined.

The data in this table reveal that azetidine **13** is an effective catalyst for the enantioselective addition of diethylzinc to aromatic aldehydes, clearly outperforming its five-membered ring analogue **27**. This observation is in accordance with the trend for the *N*-methyl analogues **9** and **10**[10,11] (Table 1). It is interesting to note that the optimal experimental conditions reported for the application of auxiliary **27** in this reaction (10 mol%, hexane)[16] are different from those that are optimal for auxiliary **13** (20 mol%, toluene). Remarkably, higher amounts of catalyst and the use of toluene as solvent, surprisingly resulted in the case of **27** in lower selectivities. Direct comparison of the auxiliaries **13** and **27** under identical conditions (20 mol%, toluene) confirmed this (*cf.* entry 1 and 3), underlining the better inductive capacity of azetidine carbinol **13** when compared with pyrrolidine carbinol **27**.

In order to study the effect of structural alterations on the efficiency of the auxiliary, the amino alcohols **14-19** were tested in the reaction with benzaldehyde, using auxiliary **13** as the reference catalyst (Table 3).

Table 3 *The effect of structural alteration on the effectiveness of functionalised azetidines*



Auxiliary	Yield (%)	*ee* (%)[a]	confign[b]
13	62	88	R
14	60	41	R
15	85	95	R
15[c]	n.d.[d]	83	R
18[c]	n.d.[d]	95	R
16	72	60	S
17	75	35	S
19	n.d.[d]	11	S

[a] determined by chiral capillary GC using BetaDEX™ by Supelco.
[b] based on optical rotation. [c] 5 mol%. [d] not determined.

As expected, reduction of the steric bulk of the α-substituent by replacement of the diphenylhydroxymethyl moiety by a primary alcohol function, significantly reduces the efficiency of the auxiliary as can be deduced from the notably lower selectivity (*cf.* entry 1 and 2). On the other hand, the introduction of a second stereogenic centre, *viz.* through the (*S*)-α-methylbenzyl group as nitrogen substituent, enhances the inductive capacity of the auxiliary, as the enantioselectivity is improved to approximately 95% (entry 3). Apparently, the presence of the aromatic tertiary alcohol plays a crucial role in the stereoselectivity of the reaction. Similar observations for the 'magic' diarylhydroxymethyl group have been made in various other asymmetric processes[17].

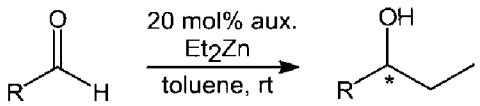
The introduction of the bulky trityl group as nitrogen substituent does not lead to an improvement of enantioselectivity. It should be emphasised that for **18** 5 mol% of catalyst is used, as compared to 20 mol% in the case of catalyst **15**. Since reduction of the amount of **15** results in a significantly lower selectivity, the conclusion is justified that azetidine carbinol **18** is the most efficient catalyst and seemingly the bulky trityl substituent has a positive effect on the chirality transfer in the diethylzinc addition reaction. The beneficial effect of a bulky nitrogen substituent was observed also in the case of aziridine derived amino alcohols as catalysts[18]. This effect however,

seems to be limited to the tertiary diphenyl alcohol, because the tritylated primary alcohol **19** exhibits almost no selectivity.

It is of interest to compare the diastereomeric catalysts **15** and **17**. Diastereomer **15** having the opposite sense of chirality at the respective stereogenic centres shows a much higher selectivity than the diastereomer **17** with the same sense of chirality at both stereogenic centres (*cf.* entry 3 and 7). This points to a matching effect on the chirality transfer in the case of **15**, while for its diasteromer **17** there is clearly a mismatch of stereogenic centres. Interestingly, for the primary alcohol **16** this mismatching effect of both stereogenic centres is much less pronounced, as this chiral auxiliary shows an appreciable selectivity compared with **17** (*cf.* entry 6 and 7). The chirality of the nitrogen substituent has no effect on the absolute configuration of the reaction product, because this is solely determined by the chiral centre at the four-membered ring. The results shown in Table

Although auxiliary **18** is inherently more effective than auxiliary **15**, the synthetic accessibility of the latter is much better, making it in practical terms the best catalyst. Therefore, auxiliary **15** was tested for some aliphatic aldehydes, the results of which are collected in table 4 .

Table 4 *Enantioselective addition of diethylzinc to aliphatic aldehydes, catalysed by* ***13***



R	Auxiliary	Yield (%)	*ee* (%)
*i*Bu	**15**	45	90[a]
c-Hexyl	**15**	80	97[a]
n-Octyl	**15**	65	83[b]
n-Octyl	**10**	--	68[11]
n-Decyl	**15**	75	77[b]

[a] det. by chiral capillary GC using BetaDEX™ by Supelco.
[b] determined by ^{19}F NMR of MPTA-ester[18].

Enantioselectivities ranging from 77-97% were obtained, which for aliphatic aldehydes may be regarded as excellent. Comparison of auxiliaries **10** and **15** (entry 3 and 4) clearly shows **15** to be the more effective catalyst, confirming the previous observations that an increase of the steric bulk of the nitrogen substituent, results in a more effective catalyst.

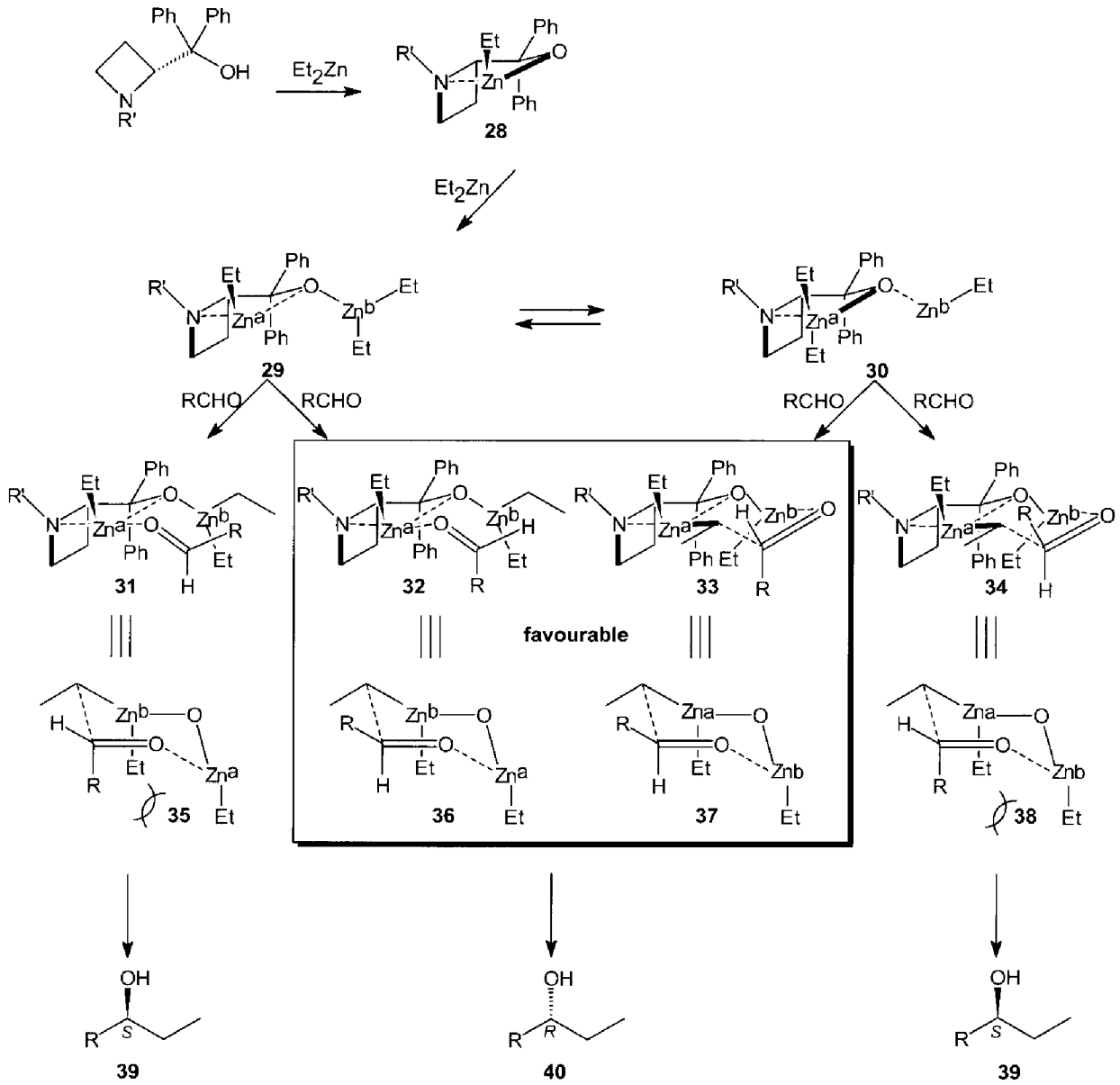
5.5 Mechanistic considerations

It is tempting to rationalise the stereochemical outcome of the asymmetric addition of diethylzinc to aldehydes in terms of the catalytic cycle depicted in Scheme 1 by a comparison of the respective transition states leading to the enantiomeric addition products. In this context it would be highly desirable to gain some insight in the 'magic' diarylhydroxymethyl effect, the role of the substituent at nitrogen and the influence of the ring size of the heterocyclic catalyst. The main features of the catalytic cycle are mechanistically well understood as already mentioned in section 5.1. However, the stereochemical aspects of the addition reaction are less clear. In recent years transition state models have been proposed[16,19] on the basis of experimental observations and supported by molecular modelling[19e,f]. So far, these models are insufficiently capable of explaining the structural effects of the catalysts on the asymmetric addition reaction. This is however, not too surprising because of the small energy differences between the transition states leading to the enantiomeric products. Subtle structural changes may have a substantial effect on the stereochemical outcome as is also apparent from comparison of the catalysts that were used in this study.

In order to explain the stereochemical results obtained for the azetidine derived catalysts a slightly modified version of one of the literature models for the transition state will be used (Scheme 6). This model has been used previously for related heterocyclic amino alcohols as the catalyst in the diethylzinc reaction[19b].

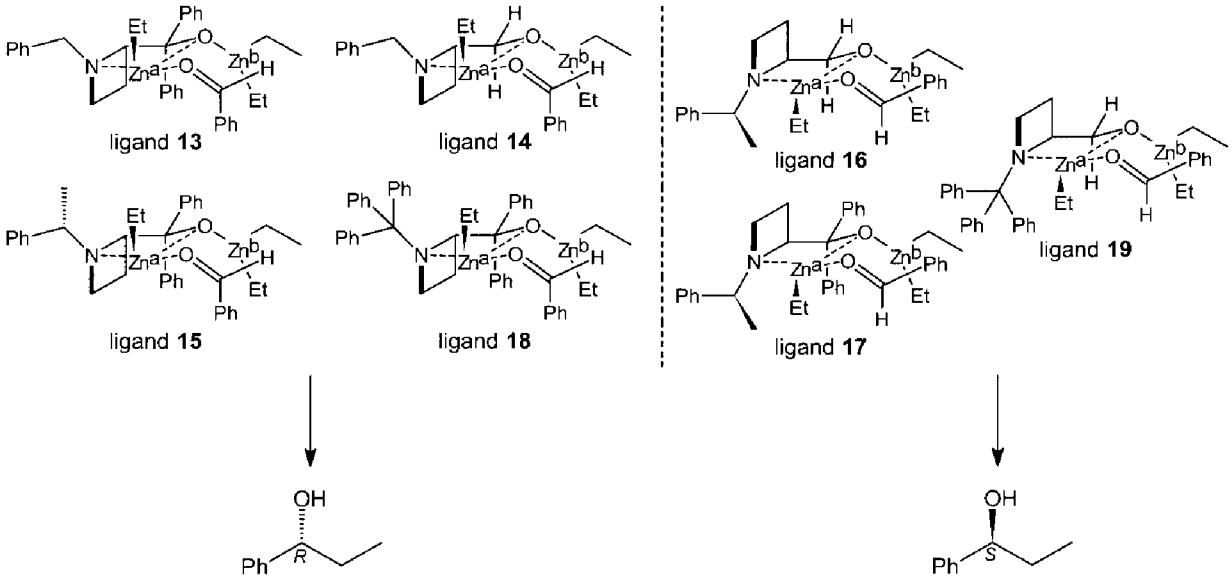
In analogy with Scheme 1 species **28** may be considered as the actual catalyst (compare species **2** in Scheme 1). Addition of a second molecule of diethylzinc leads to complexes **29** and **30** which are the equivalent of the species **3** and **4** (Scheme 1). Two modes of co-ordination of the aldehyde with these catalytic complexes can be envisaged, *viz.* **30-34**, involving both enantiotopic faces of the aldehyde (compare complexes **5** and **5'** in Scheme 1). For the sake of clarity the non relevant substituents have been omitted and the model has been slightly turned to clearly demonstrate the two different transition states, **35** *vs* **36** and **37** *vs* **38** respectively, for the aldehyde reaction. Considering the steric effects in these chair-like six-membered ring transition states, the co-ordination modes **32** and **33** are much more favourable than that of **31** and **34**, especially due to steric hindrance of the ethylzinc substituent with the substituent at the aldehyde carbon atom. The pseudo-equatorial orientation of the aldehyde substituent in **36** and **37** induces less steric hindrance than in **35** and **38** where this substituent holds a pseudo-axial position. These transition state complexes **32** and **33** lead to the (*R*) alcohol **40** which is the predicted predominant reaction product.

Scheme 6 *Working model of the transition state of the diethylzinc addition to aldehydes, catalysed by amino alcohols* **13,15** *and* **18**



Application of this model to the amino alcohols **13-19** readily explains the observed stereochemical outcome of the asymmetric diethylzinc addition to aldehydes catalysed by the azetidine carbinols **13-19** (Figure 2). Ligands **13-15** and **18** yield the same addition product, while the use of amino alcohols **16, 17** and **19** with opposite stereochemistry at the heterocyclic ring, results in a reversal of stereochemistry of the resulting secondary alcohol.

Figure 2 *Transition states for the asymmetric Et_2Zn addition to benzaldehyde catalysed by azetidine carbinols* ***13-19***



Although the sterochemical outcome of the addition reaction is readily explained by these transition state models, the observed 'magic' diphenylhydroxymethyl effect, the role of the substituent at nitrogen and the influence of the ring size of the heterocyclic catalyst are less obvious. The transition state models suggest a steric interaction between one of the phenyl groups and the ethyl group co-ordinated to one of the zinc atoms (Zn_B), which forces the diethylzinc moiety in the direction of the aldehyde (transition state model **32**) and creates a certain rigidity of the transition state. The absence of the diphenylhydroxymethyl effect in the case of amino alcohol **17** however, remains unexplained. The impact of the nitrogen substituent on the asymmetric induction may also be explained by steric factors, as increase of the steric bulk results in a considerable increase of enantioselectivity of the reaction. Although this substituent is to remote from the aldehyde to cause a direct steric interaction, an indirect interaction may be anticipated. With increasing size, the steric repulsion between the nitrogen substituent and the pseudo-axial ethyl substituent of the endocyclic zinc (Zn^a) atom will become more pronounced. As a result, this ethyl substituent will tend to move away in the opposite direction which causes an increasing interaction with the aldehyde substituent, making transition state **32** increasingly favourable over **31**. Hence, an increase of enanantioselectivity will be observed.

A final aspect that needs rationalisation, is the influence of the ring size of the auxiliary on the stereochemical outcome of the reaction. In general, this was

anticipated from the onset of the experiments, as conformational rigidity of the auxiliary was expected to result in more rigid and compact transition states and hence improved selectivity. How this idea of increased rigidity fits into the proposed transition state models however, is not clear.

5.6 Concluding remarks

The results described in this chapter clearly reveal that azetidine derived amino alcohols can serve as efficient catalysts in the asymmetric addition of diethylzinc to aldehydes. This finding confirms that conformational rigidity of the chiral auxiliaries has a beneficial effect on the chiral induction exerted by these catalysts. The rigid azetidine derived amino alcohols **13**, **15** and **18** are effective and efficient catalysts in the enantioslective addition of diethylzinc to both aromatic and aliphatic aldehydes, whereby catalyst **15** clearly outperforms its five-membered ring analogue.

By varying the substitution pattern of the azetidine carbinols it was found that the configuration of the secondary alcohol which is the result of this asymmetric addition reaction, is solely determined by the stereochemistry of the azetidine ring. The introduction of a second stereogenic centre in the substituent at the azetidine nitrogen atom has no effect on the absolute cofiguration of the alcoholic product. However, the extent of chiral induction is affected by the chiral sense of the stereogenic centre of the nitrogen substituent, either a match or mismatch with chirality transfer of the azetidine chiral centre may occur.

Structural fine-tuning revealed that the presence of a diarylhydroxymethyl group, preferable in combination of a sterically demanding nitrogen substituent, is essential for a high asymmetric induction. These observations, together with the stereochemical outcome of the addition reaction could be rationalised using a working model of the possible transition states, assuming an (indirect) repulsion between the incoming aldehyde and the nitrogen substituent as well as between the alcohol moiety and the exocyclic diethylzinc. A similar working model has previously been used to explain the efficiency of other heterocyclic amino alcohols in this reaction.

The azetidine derived amino alcohols show a better induction performance than the corresponding five-membered rings. This may be attributed to their increased conformational rigidity which results in less flexible transition states. How this fits into the proposed working models however, remains unclear.

5.7 Experimental Part

General remarks

Melting points were determined using a Reichert thermopan microscope and are uncorrected. Optical rotations were measured with a Perkin Elmer automatic polarimeter, model 241 MC, using concentrations *c* in g/100 ml at 20 °C in the solvents indicated. ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AC 100 (100 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer. The chemical shift δ is given in ppm relative to the internal standard (TMS for ^{1}H-NMR, $CDCl_3$ for ^{13}C-NMR). IR spectra were recorded on a Perkin Elmer 298 spectrophotometer. The wavenumber ν is listed in cm^{-1}. For (high resolution) mass spectra a double focussing VG7070E mass spectrometer was used. GC-MS were measured using a Varian Saturn II GC-MS by on-column injection (DB-1 column, length 30 m, internal diameter 0.25 mm, film thickness 0.25 μm). Elemental analyses were performed using a Carlo Erba Instruments CHNS-O EA 1108 element analyzer.

Chemicals

Diethyl ether was pre-dried over calcium chloride, then distilled from calcium hydride and stored over 4 Å molsieves. Hexane and ethyl acetate were distilled from calcium hydride and stored over 4 Å molsieves. All other reagents were analytical grade and used as such.

Synthesis of azetidine derived amino alcohols

The amino alcohols **15-17** and **27** have previously been described[14,22] and were prepared accordingly.

Diphenyl-(1-benzylazetidin-2*R*-yl)methanol 13

To an ice-cooled solution of methyl 1-benzylazetidine-2*R*-carboxylate[14] (2.0 g, 9.7 mmol) in diethyl ether (10 ml) an ethereal solution of PhMgBr (17 ml, 5 equiv.) was added gradually. The solution was stirred at ambient temperature until TLC (hexane : ethyl acetate 4 : 1) showed completion of the reaction. The reaction was quenched by the addition of an excess of a saturated aqueous NH_4Cl solution and the water layer was subsequently extracted with diethyl ether (3x 50 ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane : ethyl acetate 4:1), to give 2.7 g (87 %) of **13** as a white solid, mp 133-135 °C, $[\alpha]_D^{20}$ -37.7° (*c* = 1, $CHCl_3$).. ^{1}H NMR (100 MHz, $CDCl_3$) δ : 2.14 (m, 2H, $CHCH_2CH$), 2.85 (ddd, 2H, NCH_2), 3.09 (s, 2H, CH_2Ph), 3.20 (m, NC*H*), 4.39 (t, ^{3}J = 7.8 Hz, 1H, C*H*$(Ph_2)OH$, 5.29 (s, 1H, O*H*), 7.07-7.65 (m, 15H, 3x C_6H_5). ^{13}C (75 MHz) δ: 19.8 ($CHCH_2CH$), 50.7 (NCH_2), 61.7 (NCH and CH_2Ph), 72.5 ($C(Ph)_2OH$), 126.1 ($C_{Ar}H$), 126.2 ($C_{Ar}H$), 127.0 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 140.6 (C_{Ar}), 145.3 (C_{Ar}), 148.1 (C_{Ar}). IR ($CHCl_3$) ν: 3450.

1-Benzyl-2*R*-hydroxymethylazetidine 14

A solution of methyl 1-benzylazetidine-2*R*-carboxylate[15] (1.0 g, 4.9 mmol) in diethylether (5 ml) was added dropwise to an ice-cooled suspension of $LiAlH_4$ (200 mg, 5.27 mmol) in dry diethyl ether. The mixture was stirred for 1 hour and then quenched by the careful addition of water. The mixture was filtered and the residue thoroughly washed with diethyl ether. The combined washings were dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography (hexane : ethyl acetate 4:1), to give 870 mg (95%) of **14**

as a colourless oil, $[a]_D^{20}$ -30.2° (*c* = 1, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$) δ : 1.93 (m, 1H, CHC*H*$_2$CH), 2.20 (m, 1H, CHC*H*$_2$CH), 2.93 (ddd, 1H, NC*H*$_2$) 3.29 (m + s, 3H, NC*H*$_2$ and C*H*$_2$OH), 3.41 (m, 1H, NC*H*), 3.63 (dd, J_{AB} = 12.7 Hz, 2H, C*H*$_2$Ph), 7.28 (m, 5H, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$) δ : 15.9(CH_2), 48.7 (CH_2OH), 59.2 and 59.4 (NCH_2 and CH_2Ph), 64.0 (NCH), 124.6 ($C_{Ar}H$), 125.7 ($C_{Ar}H$), 126.0 ($C_{Ar}H$), 135.4 (C_{Ar}). IR ($CHCl_3$) ν: 3450.

Diphenyl-[1-tritylazetidin-2*R*-yl]methanol 18

Palladium hydroxyde on carbon (191 mg, 25 mol%) was added to a solution of diphenyl-((1*S*)-phenylethyl)azetidin-2*R*-yl)-methanol **15** (260 mg, 0.76 mmol) in methanol (20 ml).The suspension was placed under a hydrogen atmosphere (50 atm) in an autoclave. After stirring for 24 hours at 50 °C, the catalyst was removed by filtration over hyflo and the solution concentrated *in vacuo*. The debenzylated alcohol was dissolved in chloroform and the solution was cooled in ice. To this solution was successively added, triethylamine (0.11 ml, 1.1 equiv.) and a solution of freshly prepared trityl chloride (220 mg, 0.79 mmol) in chloroform. The solution was stirred at ambient temperature until TLC (hexane : ethyl acetate 4:1) showed completion of the reaction. The mixture was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (heptane : ethylacetate 4:1), to give 40 mg (11%) of **18** as a white crystalline material, mp 86 °C. $[a]_D^{20}$ -84.6 ° (*c*=1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ : 1.68 (m, 2H, CH_2CH_2CH), 3.04 (ddd, 1H, NC*H*$_2$), 3.65 (ddd, 1H, NC*H*$_2$), 4.45 (dd, 1H, NC*H*), 5.16 (s, 1H, O*H*), 6.88-7.46 (25H, arom.). NMR (75 MHz, $CDCl_3$) δ : 19.2 (CH_2), 46.5 (NCH_2), 67.1 (NCH), 77.8 ($C(Ph)_2OH$), 82.0 (CPh_3), 125.4 ($C_{Ar}H$), 125.6 ($C_{Ar}H$), 126.0 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 129.5 ($C_{Ar}H$), 142.8 (C_{Ar}), 146.9 (C_{Ar}), 147.0 (C_{Ar}). IR ($CHCl_3$) ν : 3450 (OH)

[1-tritylazetidin-2*S*-yl]methanol 19

Amino alcohol **19** was prepared analogously to **18**, starting from [(1*S*)-phenylethyl)azetidin-2*S*-yl]-methanol **16** (800 mg, 4.18 mmol), yielding after purification 128 mg (9.3%) of **19** as a colourless oil. $[a]_D^{20}$ 25.3 ° (*c*=1, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$) δ : 1.44 (m, 1H, CHC*H*$_2$CH), 1.99 (m, 1H, CHC*H*$_2$CH), 2.74 (ddd, 1H, NC*H*$_2$), 3.29 (ddd, 1H, NC*H*$_2$), 3.43 (m, 3H, NC*H* and C*H*$_2$OH), 5.28 (s, 1H, O*H*), 7.16-7.54 (m, 15H, 3x C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$) δ : 18,5 (CH_2), 45.5 (CH_2OH), 61.6 (NCH), 64.9 (NCH_2), 81.9 (CPh_3), 126.4 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 129.4 ($C_{Ar}H$), 143.0 (C_{Ar}). IR ($CHCl_3$) ν: 3420.

Enantioselective diethylzinc additions

General procedure

The appropriate ligand (20 mol%) was dissolved in dry toluene (15 ml) and the aldehyde (5 mmol) was added. The reaction mixture was cooled to 0 °C before addition of diethylzinc (10 ml, 10 mmol) and then stirred overnight at ambient temperature. The reaction mixture was quenched by adding saturated aqueous ammonium chloride solution (5 ml) and the product was extracted with ether. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/ethyl acetate 4:1 (v/v)).

Determination of enantioselectivity

The enantioselectivity was in most cases determined by chiral capillary GC analysis (BetaDEX™ 120 fused silica column by Supelco) of the obtained alcohols. In the case of 1-cyclohexyl-1-propanol, 3-undecanol and 3-tridecanol the corresponding (+)-α-methoxy-α-trifluoromethyl-penylacetic esters were prepared and analysed by ^{19}F NMR. The configuration of the products was established by comparison of their absolute optical rotation with literature values.

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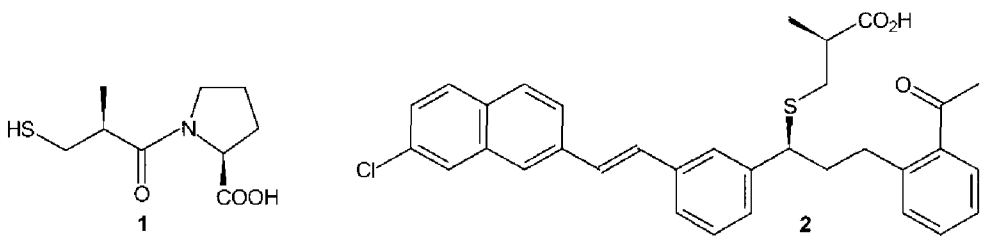
6 Diastereoselective conjugate addition of sulphur nucleophiles to chiral methacrylic amides

6.1 Introduction

Hypertension is a common and usually progressive disorder, which, if not properly treated, results in a greatly increased probability of coronary thrombosis, strokes and renal failure[1]. Therefore, the development of antihypertensive drugs has been the aim of extensive pharmaceutical research and since the 1950s enormous progress has been made in this area. These drugs can be divided into seven classes, each focusing on a specific target in the complex cascade of reactions that regulate blood pressure[2]. The so-called Angiotensin-Converting Enzyme (ACE) inhibitors constitute one class of these drugs. These drugs reversibly inhibit ACE, a carboxy peptidase that catalyses the conversion of the biologically inactive peptide angiotensin I into angiotensin II which is a very potent vasoconstrictor agent and also the main physiological stimulus for the release of aldosterone from the adrenal gland. This hormone, in turn, induces sodium and water retention, which results in an increase of blood pressure[3]. ACE also catalyses the inactivation of the vasodepressor bradykinin[3,4] and as a consequence prevents a decrease of the blood pressure. A controlled inhibition of ACE will result in a lowering of the blood pressure and hence can be used to regulate blood pressure as part of a treatment of hypertension. The first successful ACE-inhibitor was (S)-1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline or captopril **1**. Later on several other effective ACE-inhibitors were developed. The enormous demand for effective anti-hypertensive drugs is illustrated by the fact that two of them, including the ACE-inhibitor enalapril, are among the ten best sold drugs, with a total annual worldwide sales of $3.9 billion[5].

Figure 1 *Two mercapto propanoic acid containing drugs*



It is interesting to note that the development of captopril was one of the first examples of a successful *ab initio* drug design, based on detailed chemical knowledge of the active site of a target enzyme and its natural substrate. The design was further facilitated by the observation that several small peptides, isolated from the venom of the South American snake *Bothrops jararaca*, are weak inhibitors of the enzyme. Thus, captopril was designed in such a manner that it combines the steric properties of these peptide antagonists in a non-peptide molecule. A sulfhydryl group was incorporated in an appropriate position to bind the zinc atom known to be present in the active site. Furthermore, a proline residue was included that binds the site of the enzyme that normally accommodates the terminal leucine of angiotensin I[1,6].

The synthesis of captopril typically is achieved by the coupling of an appropriately thio-protected, (*S*)-3-mercapto-2-methyl-propanoic acid with L-proline[6b,7]. The use of the (*S*)-enantiomer is essential, as coupling of the corresponding (*R*)-enantiomer leads to a product that is at least 100 times less active than captopril itself[6a]. The enantiomerically pure 3-mercapto-2-methyl-propanoic acid is a structural motif that is also encountered in other pharmacologically active compounds, *e.g.* LTD_4 antagonist L-699,392 **2**[8] and is usually obtained *via* a resolution of racemic material. Such a resolution can either be achieved in a classical fashion in the stage of the acid by the fractional crystallisation of diastereomeric salts derived from various optically pure amines[7,9], or by an enzymatic, enantioselective hydrolysis of the corresponding ester[10]. These processes however, are, especially from an industrial point of view, not always satisfactory. The classical resolution is hampered by the often small difference in solubility of diastereomeric salts of the β-mercapto acids[11]. Furthermore, large amounts of expensive resolving agents are required which are often difficult to remove and left behind as an impurity in the product. Moreover, the efficiency of the processes is poor because racemisation of the undesired (*R*)-enantiomer is accompanied by substantial decomposition of the material, although some improvements have been reported[11]. The aforementioned problems can in principle be circumvented by an asymmetric synthesis of (*S*)-3-mercapto-2-methyl propanoic acid.
The research described in this chapter was aiming at such an asymmetric synthesis using an azetidine derived auxiliary.

6.2 Formal stereoselective synthesis of 3-mercapto-2-methyl-propanoic acid by an asymmetric protonation

6.2.1 Introduction

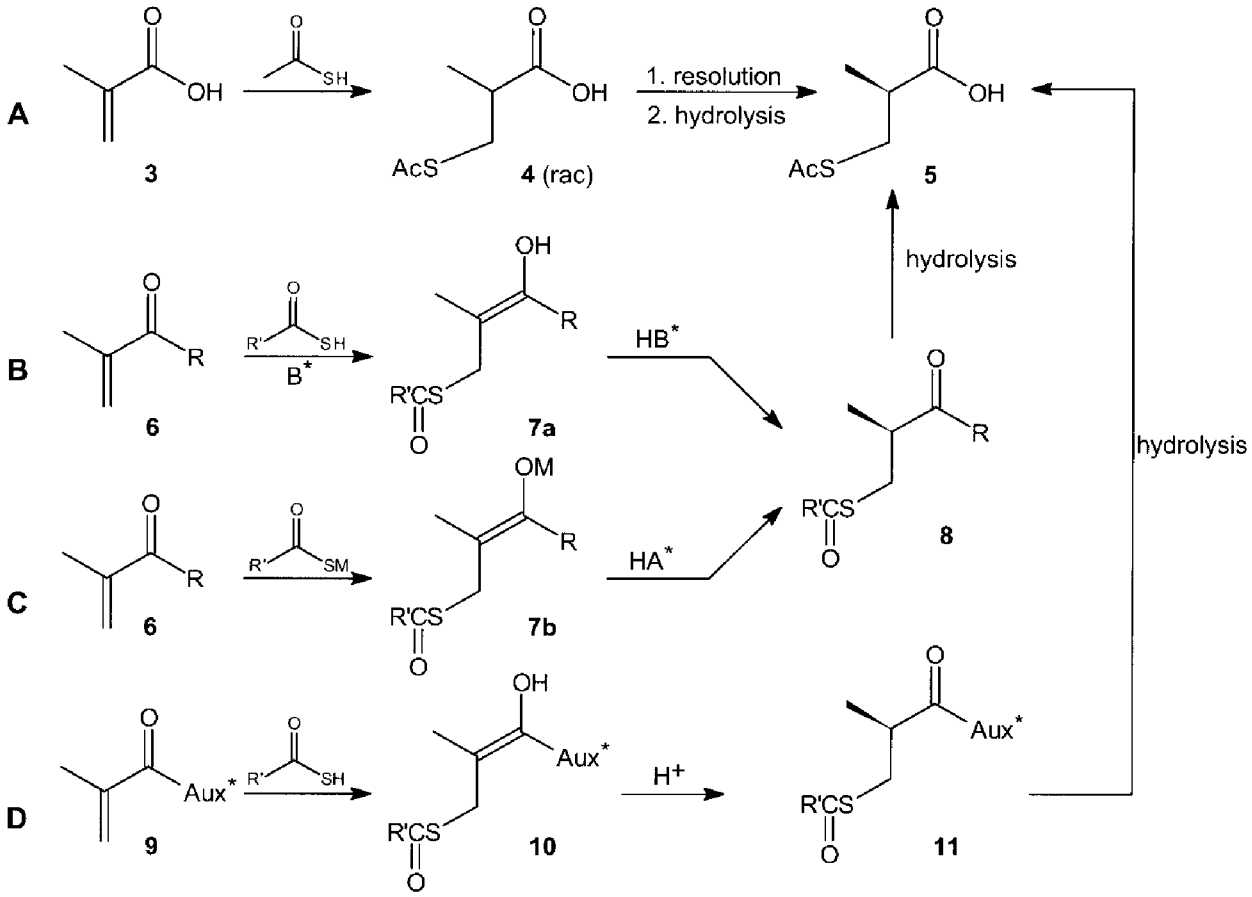
The most straightforward racemic synthesis of 3-mercapto 2-methyl propanoic acid **4** is achieved by a Michael addition of sulfur nucleophiles to methacrylic acid **3** (scheme 1, **A**). An elegant manner to convert this Michael addition into an asymmetric one, would be to induce a stereoselective protonation of the initially formed ester enolate (or enol).

Conceptually, the asymmetric protonation of enols and enolates is simple. Depending on the actual substrates, the prochiral enol has two enantiotopic or diastereotopic faces. Transfer of a proton from a (chiral) proton donor may kinetically favour either the top or bottom face, thus producing the carbonyl compound with one of its stereisomers in excess.

Despite this conceptual simplicity and the potential synthetic scope of stereoselective protonation, until recently this subject has received relatively little attention[12,13], when compared to other asymmetric processes, *e.g.* asymmetric alkylation. In fact, the first publication on asymmetric protonation reactions appeared in the literature[14] almost 75 years after the first report on asymmetric synthesis[15]. Several reasons for this apparent lack of interest can be indicated, the most important one probably being the fact that proton exchange reactions belong to the most rapid, often diffusion controlled[16] reactions, thus hampering an efficient discrimination between two diastereomeric transition states. This implies that it will be difficult to control the stereochemical outcome of protonation reactions. This protonation is further complicated by the flexible nature of enolates, *e.g.* due to *E*/*Z* isomerisation, which at least doubles the number of possible transition states. Moreover, the concept of asymmetric protonation is poorly understood as detailed information concerning transition states is lacking, especially due to the complexity of enolate chemistry[17]. As will be discussed in section **6.3**, solvation, aggregation and complexation phenomena enormously influence the outcome of the reaction. Thus, the sensitivity to subtle changes in the experimental conditions, *e.g.* temperature, solvent *etc.*, often makes the stereochemical outcome of the reaction difficult to explain and even more difficult to predict. This makes a rational design of an asymmetric protonation reaction, by choosing a suitable solvent, proton donor, temperature *etc.*, extremely difficult. Understandably, the results of asymmetric protonation of enolates often were very poor. However, since the late 1970s and early 1980s, much progress has been made in this area and several examples are now known of synthetically useful asymmetric protonations of enolates[12,13].

The stereoselective synthesis of (*S*)-3-mercapto-2-methyl-propanoic acid **5** using an asymmetric protonation reaction can be achieved in two fundamentally different ways. The first and most attractive way is an *enantioselective* synthesis of **5** (scheme 1, **B**,**C**).

Scheme 1 *Classical (route* **A***) and asymmetric (route* **B-D***) synthesis of* **5**



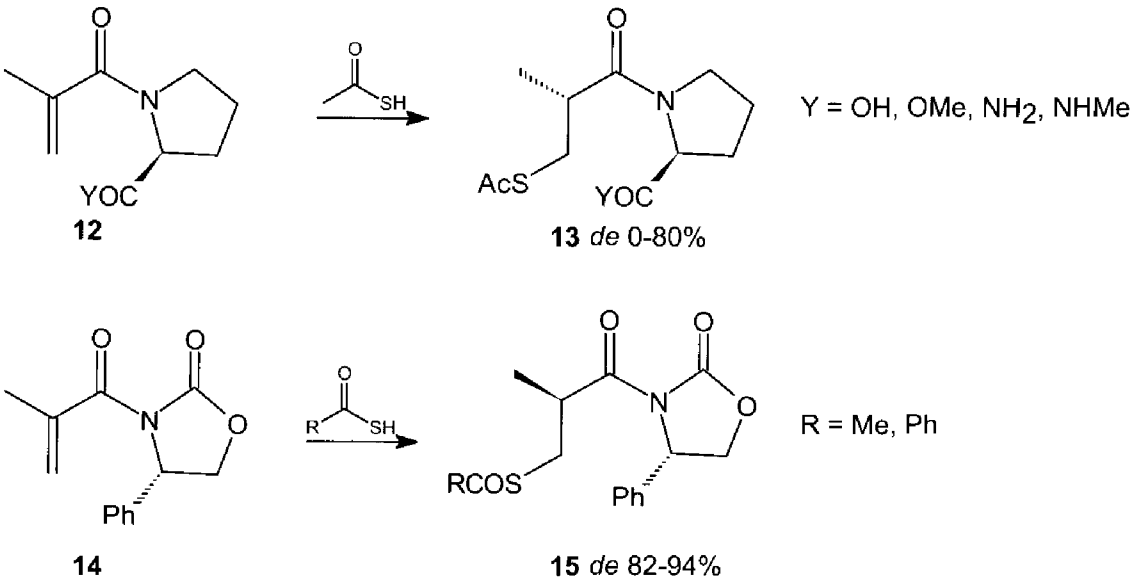
The first attempted enantioselective approach is the addition of thiocarboxylic acids to methacrylic esters catalysed by a chiral base (route **B**). The stereodetermining protonation of enol **7a** in this approach takes place by the conjugated acid of the catalytic base. The advantages of this approach are that only a catalytic amount of chiral inductor is required and that the reaction is carried out under salt-free conditions. Asymmetric Michael additions of thiols to α-substituted acrylates catalysed by cinchona alkaloids have been reported[18] and have also been applied to various methacrylic esters. The enantioselectivities obtained with these alkaloids however, were only moderate, with a maximum *ee* of 27% (R=SEt)[18a].

Alternatively, thioacetate can be used as the nucleophile, with an external chiral acid as the proton donor (route **C**). As already briefly indicated above, a rational design of such an experiment is extremely difficult, especially as it involves enolate **7b**, rather than an enol as in the previous approach. Although several successful enantioselective protonations of enolates have been reported[13], adopting those

experimental conditions to the synthesis of **5** is no guarantee for success. The stereochemical outcome of asymmetric protonations is highly susceptible to subtle changes in the reaction conditions and the enolate substrates. Therefore, a given chiral proton donor often can only be successfully applied for a narrow range of structurally related enolates. The only guideline regarding the choice of the proton donor is that it should be a relatively weak acid (pKa 15-20) in order to allow efficient discrimination between transition states[12,19], whereby the acidity of the protonated product should be 4-6 pKa units less than the proton source in order to prevent equilibration of the product[13b]. Furthermore, the proton donor preferably should also contain substituents capable of co-ordination or chelation as this enhances the conformational rigidity of the transition state. The site from which the proton will be transferred should preferably be located near the stereogenic centre of the reagent, as the trajectory by which the proton is transferred describes more or less a straight line[12]. These prerequisites are met for many proton transfer reactions but are too general to be of practical use in choosing the right set of conditions and therefore making the enantioselective transfer process a matter of trial and error.

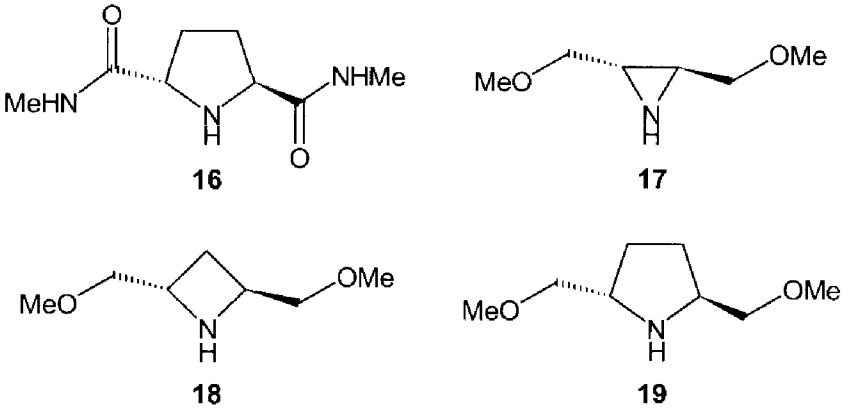
As an alternative to the rather problematic enantioselective protonation, the desired asymmetric proton transfer may also be accomplished in a *diastereoselective* fashion using substrates containing a covalently bound chiral substituent, *e.g.* esters or amides of methacrylic acid (route **D**). The presence of a stereogenic centre in the substrate leads to *diastereomeric* transition states during the proton transfer reaction, which may facilitate the chiral discrimination between the two possible products. The choice of an effective chiral auxiliary in the substrate is a very difficult one, for which no reliable guidelines are available. Conformational rigidity and chelating or co-ordinating substituents are general features encountered in successful chiral proton transfer reactions.

The diastereoselective addition of thiocarboxylic acids to chiral methacrylic amides has already been investigated in the late 1980s, using proline derivatives. In view of the desired endproduct this is the most logical choice. Effenberger *et al.* obtained diastereoselectivities of up to 80% [20] (Scheme 2). More recently, Wu *et al.*[21] reported even better results for the addition of both thioacetic and thiobenzoic acid to methacrylic amide **14**, containing an oxazolidinone substituent originally developed by Evans, as the chiral auxiliary.



Scheme 2 *Diastereoselective addition of thiocarboxylic acids to chiral methacrylic amides.*

Effenberger *et al.*[20] briefly mention that the use of the C_2-symmetric pyrrolidine **16** as a chiral auxiliary, further improves the diastereoselectivity, even to the extent that the addition product is obtained as a single diastereomer.

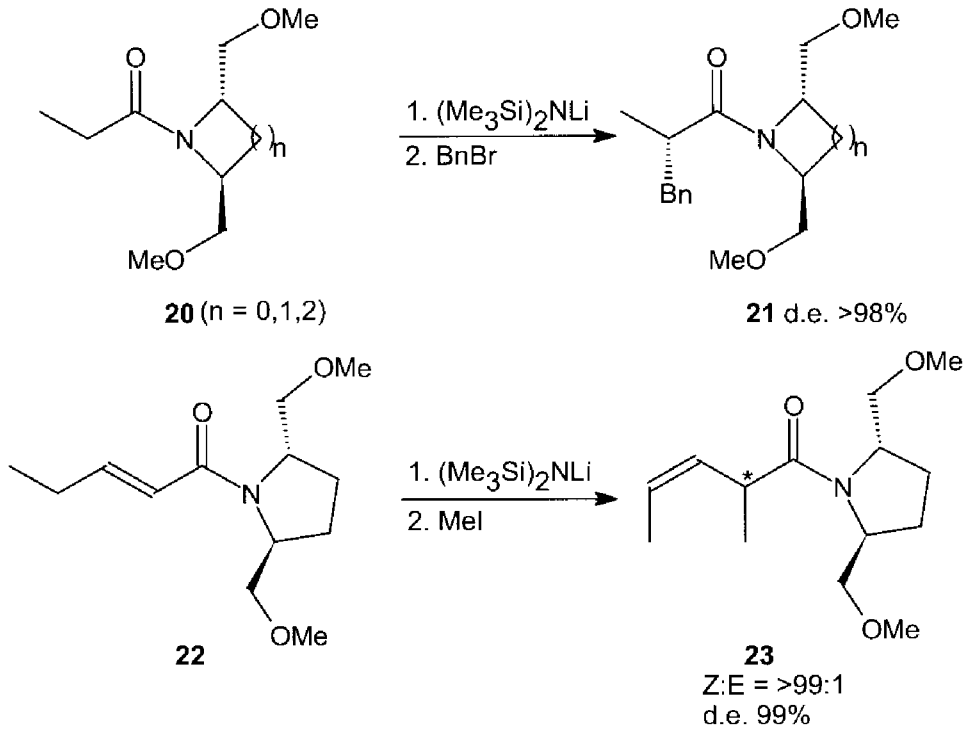


The presence of a C_2-symmetry axis within a chiral auxiliary - how antithetical it may seem with regard to the objective to achieve *asymmetric* synthesis - often contributes to a large extent to the successful outcome of a stereoselective proces. This positive effect of this symmetry element is attributed to the reduction of the number of possible competing diastereomeric transition states[22].

In view of the successful chiral induction observed for auxiliary **16**, it was a logical extension to investigate the effectiveness of other readily available related C_2-symmetric heterocyclic auxiliaries in the same reaction. For this purpose, the auxiliaries **17-19** were chosen, as they combine three characteristics that promote high asymmetric induction, *viz. conformational rigidity, potentially co-ordinating or*

chelating substituents and C_2-*symmetry*. These heterocycles already have successfully been applied as chiral auxiliary in other asymmetric processes[23], including the diastereoselective alkylation of enolates[23e-g] (Scheme 3). It should be noted however, that an asymmetric alkylation of enolate is easier to accomplish than an asymmetric protonation.

Scheme 3 *Highly diastereoselective alkylation of C_2-symmetric enolates*



For the present study, *i.e.* the diastereoselective Michael addition of thiocarboxylic acid to an appropriate chiral deriviative of methacrylic acid, amides derived from the three- and four-membered C_2-symmetric amines **17** and **18** are promising candidates. The removal of the chiral auxiliary, after completion of the Michael addition, can readily be accomplished in the case of the aziridine derived amides as can be deduced from a relevant literature report[23e] and probably in such a manner that no racemisation of the newly installed stereogenic centre takes place. The research efforts in this chapter are devoted to the use of small-ring hetereocyclic amines as chiral auxiliary in asymmetric Michael additions.

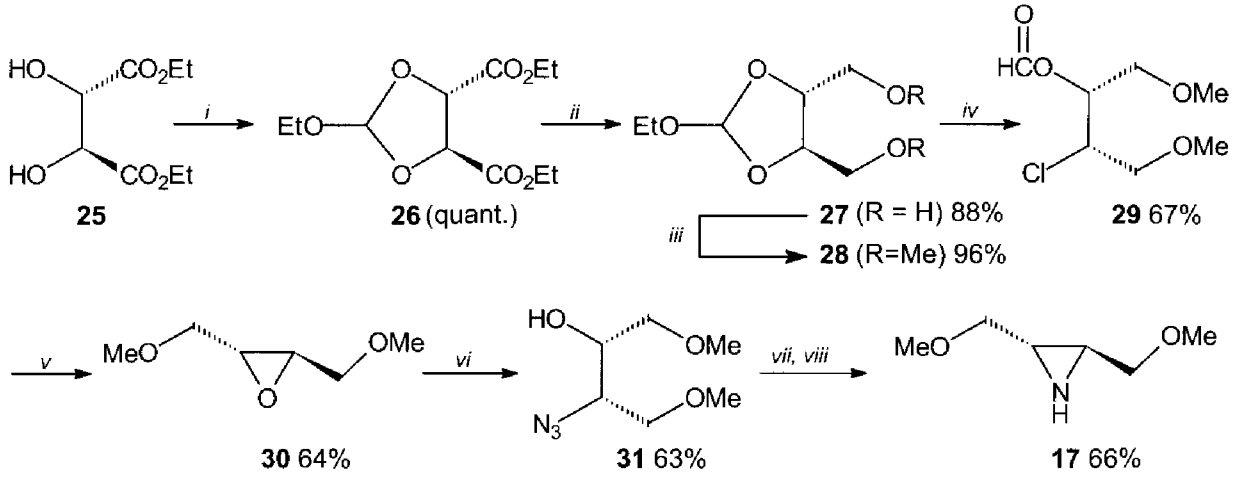
6.2.2 Synthesis of chiral methacrylic amides 24a-c

Chiral methacrylic amides can be prepared by an appropriate coupling reaction of the acrylic acid with the small-ring heterocycles **17-19**.

Aziridine **17** was prepared from (L)-diethyl tartrate following a procedure developed by Tanner *et al.*[23e] (Scheme 4). Thus, protection of the diol moiety of (L)-diethyl tartrate **25** as orthoformate, reduction of the esters and subsequent methylation gave

28 in 80% overall yield. Treatment of **28** with phosphorus pentachloride at low temperature smoothly gave chloroformate **29**, which upon base treatment gave the epoxide **30** in 43% yield[24]. Nucleophilic opening of this epoxide with sodium azide gave azido alcohol **31**, which after mesylation and careful reduction of the azido function cyclises to the desired aziridine **17** in an overall yield of 16%.

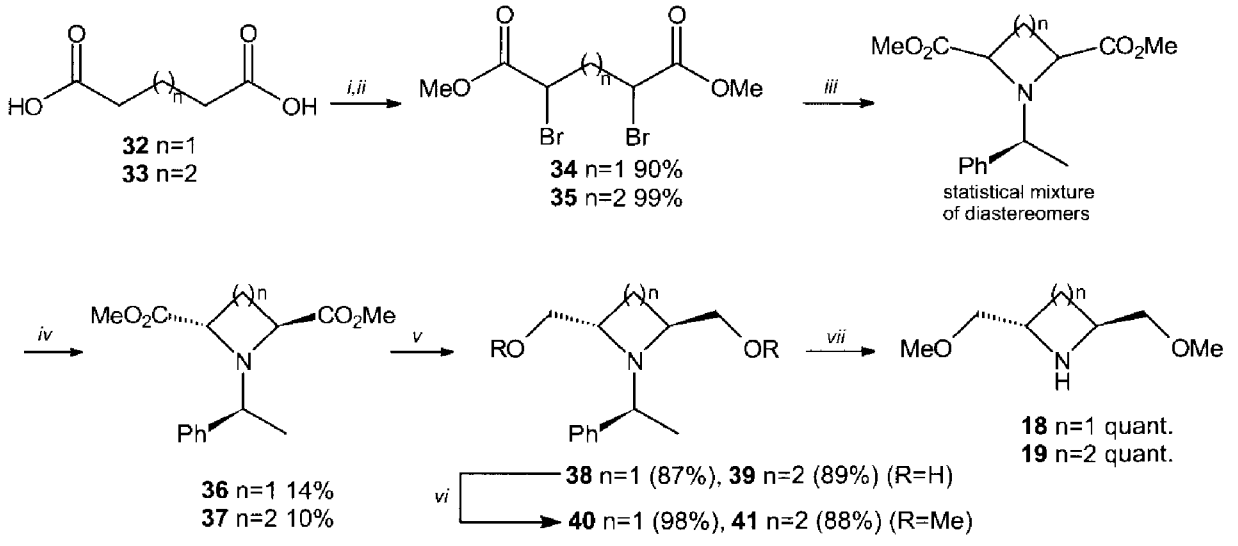
Scheme 4 *Synthesis of aziridine* **17**



(*i*) $HC(OEt)_3$, AcOH ; (*ii*) $LiAlH_4$; (*iii*) NaH, MeI ; (*iv*) PCl_5 ; (*v*) K_2CO_3 ; (*vi*) NaN_3 ; (*vii*) MsCl, Et_3N ; (*viii*) $LiAlH_4$, reflux

The synthesis of the heterocycles **18** and **19** was achieved as depicted in scheme 5[23f,25].

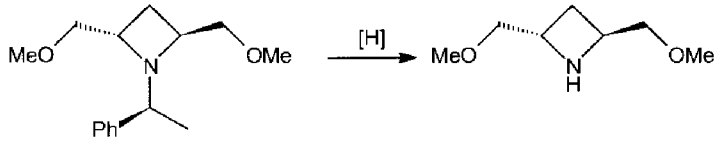
Scheme 5 *Synthesis of heterocycles* **18** *and* **19**



(*i*) P, Br_2 ; (*ii*) MeOH ; (*iii*) (*S*)-α-MBA, K_2CO_3 ; (*iv*) column chromatography ; (*v*) $LiAlH_4$; (*vi*) NaH, MeI ; (*vii*) 50 atm H_2, 25 mol% $Pd(OH)_2$, 50° C

Starting from glutaric acid **32** and adipic acid **33**, respectively, the desired heterocycles were obtained in a 7 step synthesis. Treatment of the acids with red phosphorus and bromine, followed by quenching of the intermediate acid bromides with methanol produced the dibromo esters **34** and **35** in excellent yield. Upon treatment with enantiomerically pure α-methylbenzyl amine under basic conditions, these esters cyclised to give the *N*-protected heterocycles as a statistical mixture of diastereomers. Careful and extensive chromatography resulted in the isolation of the desired (*S,S*)-diastereomers **36** and **37** in modest yield. These yields can be improved however, by basic epimerisation of the unwanted isomers, followed by repeated chromatography. Reduction of the ester moieties and subsequent methylation led to the ethers **40** and **41**, which only need to be debenzylated to give the desired cyclic amines. It was reported that this debenzylation proceeds smoothly by catalytic hydrogenolysis, using 25 mol % of $Pd(OH)_2$ as catalyst and 1 atm of hydrogen. This reported hydrogenation could not be repeated. It should be noted that for this removal of the α-methylbenzyl group a relatively large amount of catalyst was recommended. By taking into account that the small-ring heterocyclic amines must be used stoichiometrically, even larger amount of palladium catalyst are highly undesirable. For that reason, alternative methods to remove the nitrogen protecting group were investigated, which are listed in Table 1.

Table 1 *(Attempted) Debenzylation of azetidine* **40**



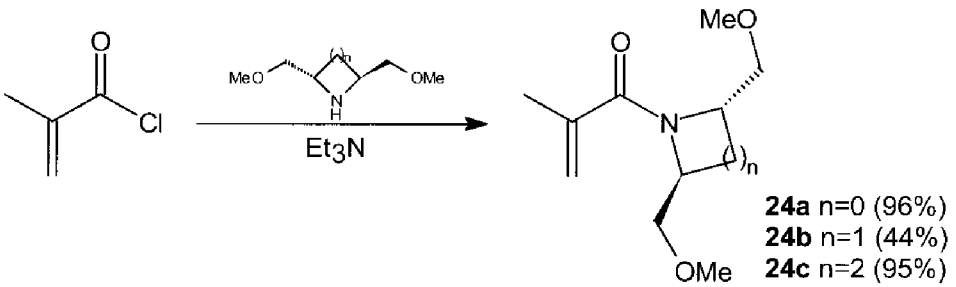
Reaction conditions	result
Li, $EtNH_2$, *t*BuOH	no reaction
Li, $EtNH_2$, THF	no reaction
mCPBA, $FeCl_2$ (Polonovski)	no reaction
H_2 (5 atm), $Pd(OH)_2$ (10 mol%), rt	no reaction
H_2 (5 atm), $Pd(OH)_2$ (25 mol%), rt	partial deprotection
H_2 (50 atm), $Pd(OH)_2$ (25 mol%), 50° C	quantitative deprotection

Initial attempts were aimed at replacing the problematic catalytic hydrogenolysis by alternative methods. However, Birch reduction conditions, previously successfully used to remove both trityl- and α-methylbenzyl[26] groups and Polonovski type conditions[27], failed to give any reaction. Reduction of the amount of catalyst, in order to make the original approach more attractive, gave no reaction. Using the reported conditions only resulted in a partial deprotection, even at moderate

hydrogen pressure. This arduous removal of the α-methylbenzyl group has been observed before in the case of analogous mono-substituted azetidines[28], where change of solvent, increasing the hydrogen pressure *etc.*, failed to give the desired deprotection. Finally, it was found that the combination of a high (50 atm) hydrogen pressure with an elevated reaction temperature (50 °C) and relatively fresh, *i.e.* wet, $Pd(OH)_2$, lead to effective conditions to achieve the desired quantitative deprotection. The use of older, completely dry batches of catalyst failed to give deprotection even under the just mentioned optimal reaction conditions. Thus, utilising these modified conditions the deprotection of both **40** and **41** was accomplished quantitatively. The overall yield of the 7 step synthesis of **18** and **19** amounted to 43 and 31%, respectively.

The required chiral methacrylic amides **24a-c** were obtained in good yield by acylation of the amines **17-19** with methacroyl chloride (Scheme 6). It is relevant to mention that the ethylbenzene formed during the hydrogenolysis is rather difficult to remove from the deprotected azetidine **18** because both compounds have similar volatility. It was therefore much more practical to perform the acylation first and then the purification. The overall yield of the combined steps is listed in Scheme 6.

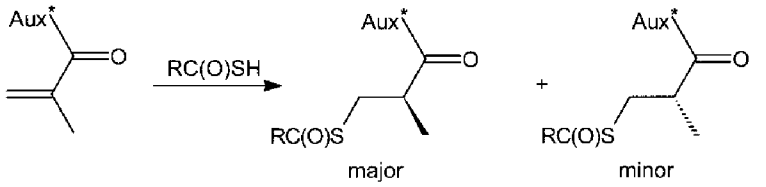
Scheme 6 *Synthesis of the chiral methacrylic amides* **24a-c**



6.2.3 Results and Discussion

The addition of thiocarboxylic acids to the methacrylic amides was initially carried out using the recommended optimal conditions for this particular reaction reported by Effenberger *et al.*, *i.e.* 5 equivalents of thioacid in dichloromethane at ambient temperature[20]. However, the results were rather disappointing. In the case of methacrylic amide **24a** a complex mixture of products was obtained, presumably due to the nucleophilic opening of the acylated aziridine ring. The addition to the methacrylic amide **24b** proceeded with a diastereoselectivity of only 77%.

Table 2 *Diastereoselective addition of thiocarboxylic acids to methacrylic amides* **24a-c**



methacrylic amide	R	equiv.	solvent	addition product	*de* (%)#	yield (%)[c]
24a	Me	5	CH_2Cl_2		--[a]	
24b	Me	5	CH_2Cl_2	**42**	77	--[d]
24a	Me	1	CH_2Cl_2		--[a]	
24b	Me	1	CH_2Cl_2	**42**	97	60
24b	Me	1	DMF	**42**	52	--[d]
24b	Me	1	toluene	**42**	97	--[d]
24c	Me	1	CH_2Cl_2	**43**	86	48
24b	Ph	1	CH_2Cl_2	**44**	91	65
24c	Ph	1	CH_2Cl_2		--[b]	--

[#] the *d.e.* was determined by capillary GC-analysis of the crude mixtures [a] complex mixture of products. [b] no reaction. [c] isolated yield of major isomer. [d] not determined.

The initially obtained unsatisfactory results may be attributed to the use of a large excess of thioacetic acid, which may cause undesired side reactions to take place. For that reason the reaction was repeated with one equivalent of thioacid. The aziridine derived methacrylic amide still gave a complex mixture of products. However, the reaction with azetidine derived methacrylic amide **24b** took place in quantitative yield with a high stereoselectivity, *viz.* with a *de* of 97%. Unfortunately, during removal of the minor diastereoisomer by column chromatography, considerable loss of material had to be accepted, ultimately giving the enantiopure major diastereoisomer **42** in 60% isolated yield. The chromatographic purification was complicated by the very small difference in R_f-value of both diastereoisomers as was apparent from TLC separation experiments.

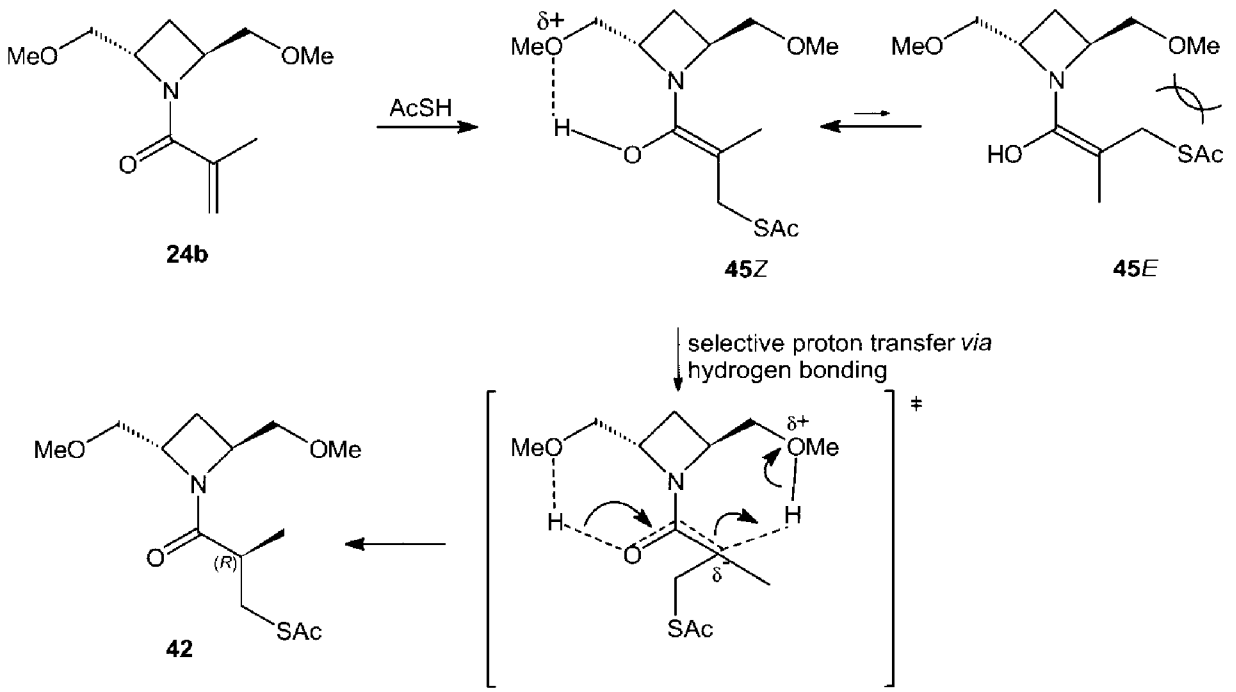
Remarkably, the addition of thioacetic acid to methacrylic amide **24c** derived from pyrrolidine **19** proceeds much slower, reaching only 36% conversion after 12 hours. More importantly, the stereoselectivity of the reaction, which was complete after 72 hours, was substantially lower than for the azetidine derived substrate. This may be caused by the long reaction time during which a slow epimerisation of the formed product takes place, as was established by monitoring the reaction by capillary GC. Initially, a single diastereomer was formed, which after 48 hours slowly began to epimerise. It should be reminded here that the asymmetric protonation step in this Michael addition reaction is a kinetically controlled process. During prolonged

reaction times, required to bring the addition to completion, racemisation by epimerisation at the α-carbon atom, which is a thermodynamically controlled process, may become a serious complicating factor. Consequently, long reaction times may be prohibitive for an efficient asymmetric protonation sequence[13b]. The remarkable difference between the methacrylic amides **24b** and **24c** was even more striking when thiobenzoic acid was used as the nucleophile in the Michael addition reaction. While in the case of **24b** the reaction reached completion after 24 hours, giving a product with a selectivity of 91%, methacrylic amide **24c** failed to give any addition reaction even after 72 hours. The highly remarkable difference in reactivity between the four- and five-membered ring containing acryl amides is difficult to understand but may be attributed to a difference in amide resonance. This amide resonance involves an exocyclic iminium bond, which is more strained in the case of a four- than for a five-membered ring. Consequently, the azetidine derived acrylic amide is more electrophilic and thus a better Michael acceptor.

The absolute configuration at C-2′ of the major diastereomeric product was determined by acid hydrolysis to give the known 3-mercapto-2-methyl propanoic acid and subsequent comparison of its optical rotation with values reported in the literature[20]. In this manner it was shown that amides with the (*S,S*)-configuration lead to products with the (*R*)-configuration at C-2′.

A tentative mechanistic explanation of the observed stereoselectivity is depicted in Scheme 7.

Scheme 7 *Mechanistic explanation of the observed diastereoselectivity in the Michael addition*



The addition of the thioacid is most likely a two step process involving an activating protonation of the methacrylic amide, followed by a Michael addition of the conjugated base[21], thereby generating the enols **45***Z* and **45***E* which, in principle, are in equilibrium. However, due to the unfavourable steric interaction between the thioacetate moiety and the heterocyclic unit in **45***E*, it is understandable that the other geometrical isomer **45***Z* having the less cumbersome steric interaction of the methoxymethyl substituent with the methyl substituent at the enol, is the predominant one. Moreover, the hydrogen bonding between the enolic hydroxyl group and the ether oxygen atom restricts the rotation about the nitrogen-carbon bond whereby the steric effect in **45***E* becomes even more pronounced. Introduction of a proton at the free methoxy group in the predominant enol **45***Z* leads to a favourable transition state for the proton transfer reaction as is shown in Scheme 7.

The proposed mechanism for the stereocontrolled proton transfer is substantiated by the observation that in apolar solvents, *e.g.* dichloromethane and toluene, a higher asymmetric induction is observed than in a polar aprotic solvent such as DMF. In the apolar medium hydrogen bonding is bridging the prochiral enolic carbon atom with the methoxy group as shown in Scheme 7. In this manner a cyclic transition state arises in which the proton is selectively transferred to the rear face of the enol, thus generating the *R*-chirality in the product. A polar solvent such as DMF will disrupt these crucial hydrogen bonds with the consequence that selectivity of the proton transfer reaction is much less efficient. This mechanism is also in full agreement with the known preferred trajectory for the C-protonation of enolates, which involves a vertical approach of the proton to the plane defined by the enolate olefinic bond, with a preferential co-linear arrangement between the donor atom, the proton and the accepting atom.[13b]. The selectivity observed during the Michael addition of thioacetic acid to the proline derived methacrylic amide **12** was explained in an analogous manner. In this case in the polar aprotic solvent DMF stereoselectivity was completely absent.

The asymmetric Michael addition shown in Scheme 7 leads to the incorrect absolute configuration for the synthesis of captopril. However, by choosing the antipode of the four-membered ring heterocycle **18** as chiral auxiliary in the methacrylic amide, the correct stereochemistry can be introduced using this methodology. The antipode of **18** can be obtained from the 2*R*,4*R* diastereomer of **36** which was produced in an equimolar quantity in the synthetic sequence shown in Scheme 5. Isolation of this particular ester is complicated by the difficult separation of this ester from the corresponding *cis*-ester. For this reason, the synthesis of the azetidine derived methacrylic amide with the correct absolute configuration was not pursued further.

It is relevant to mention that the asymmetric Michael reaction gave practically the same result in dichloromethane and toluene, the latter being preferred for environmental reasons.

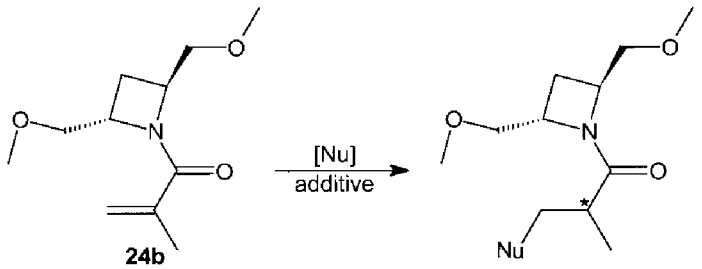
6.3 Diastereoselective addition of other sulphur nucleophiles to methacrylic amides 24b and 24c

6.3.1 Direct Michael addition reactions of thiols

In view of the excellent results obtained for the asymmetric Michael addition reaction of thioacids to methacrylic amide **24b**, its is of interest to extend the scope of this reaction to other sulphur nucleophiles. For this purpose four thiols and also thiocyanate were investigated.

Unfortunately, no addition reaction of benzenethiol[30], *p*-methoxybenzene thiol, *p*-nitrobenzene thiol and benzyl thiol was observed (Table 3, entry 1-4).

Table 3 *Attempted diastereoselective addition of sulphur nucleophiles to methacrylic amide* **24b**



[Nu]	solvent	additive	*de* (%)	[Nu]	solvent	additive	*de* (%)
PhSH	CH_2Cl_2	-	-	PhSH	CH_2Cl_2	Et_3N (cat.)	-
p$MeOC_6H_4SH$	CH_2Cl_2	-	-	PhSH	CH_2Cl_2	Et_3N (1 eq.)	-
p$NO_2C_6H_4SH$	CH_2Cl_2	-	-	PhSH	CH_2Cl_2	Li*O*tBu (cat.)	-
BnSH	CH_2Cl_2	-	-	*p*$MeOC_6H_4SH$	CH_2Cl_2	Et_3N (cat.)	-
KSCN	DMSO	-	-	*p*$MeOC_6H_4SH$	CH_2Cl_2	Et_3N (1 eq.)	-
				PhSH	CH_2Cl_2	$TiCl_4$	-
				BnSH	THF	$Yb(OTf)_3$	-

The failure of these Michael addition reactions may be attributed on one hand to the relatively poor Michael accepting capability of α,β-unsaturated amides[31] and on the other hand to the low acidity of the thiols when compared with thioacids. The amide resonance has a negative effect on the electrophilicity of the conjugated amides. The

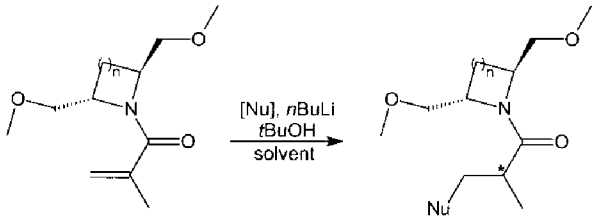
Michael addition is a two step process of which the first one is the activation of the enone system by protonation of the carbonyl group[21]. The thiols are apparently insufficiently capable of inducing such activation. Even the more acidic *p*-nitrobenzene thiol does not show any reaction.

Two attempts were made to catalyse the addition reaction. First, an external mild base, *i.e.* triethylamine or lithium *tert*-butoxide, was added to convert the thiols into the thiolates and thus enhance their nucleophilicity. However, the result was negative. Only disulfide formation was observed after prolonged reaction times (probably oxidation by air). Secondly, a Lewis acid was added, *viz.* titanium tetrachloride or ytterbium triflate, to activate the enone system, however also in vain.

6.3.2 Asymmetric Michael addition reactions of lithium thiolates

An entirely different approach involves the use of lithium thiolates as the nucleophilic species in an appropriate solvent in the presence of a suitable proton donor. This approach ensures the optimal nucleophilicity of the sulphur nucleophiles. The choice of the proton donor is a rather subtle matter. *tert*-Butyl alcohol was first chosen for this purpose. The result of this approach was highly gratifying as a Michael addition was accomplished with an appreciable diastereoselectivity for methacrylic amides derived from both azetidine **18** and pyrrolidine **19**. The results are collected in Table 4.

Table 4 *Diastereoselective Michael adition of thiols to methacrylic amides* **24b** *and* **24c** *using butyllithium and a proton donor*



24b (n=1)
24c (n=2)

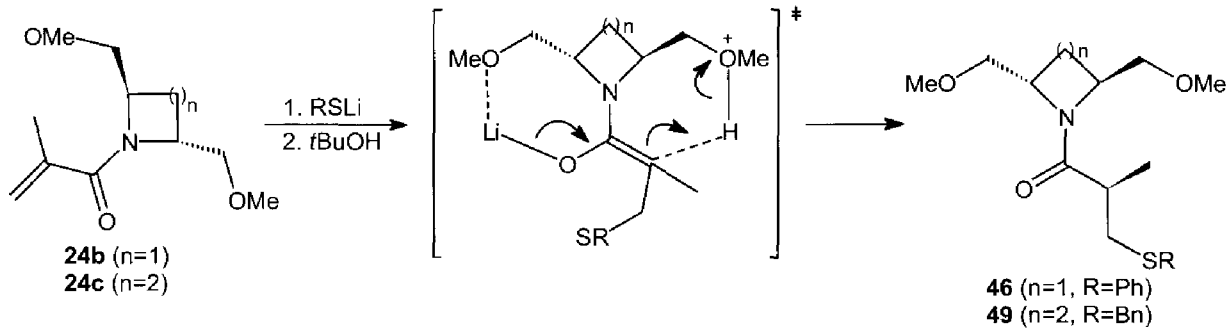
46 (n=1, Nu=PhS)
49 (n=2, Nu=BnS)

methacrylic amide	nucleophile	solvent	product	*de* (%)[a]	Yield (%)[b]
24b	PhSH	CH_2Cl_2	**46**	88	95(19[c])
24b	PhSH	toluene	**46**	74	92(25[c])
24b	PhSH	Et_2O	**46**	61	87
24b	PhSH	THF	**46**	43	93
24c	BnSH	CH_2Cl_2	**49**	77	92
24c	BnSH	toluene	**49**	78	96(18[c])

[a] determined by capillary GC analysis of the crude mixture. [b] crude yield. [c] isolated yield of the major isomer.

Butyllithium clearly converts the thiols irreversibly into the corresponding thiolates which then add to methacrylic amides in a Michael fashion. The protonation of the initially obtained lithium enolates is accomplished by the external proton donor *tert*-butyl alcohol. The amount of proton donor is critical, it should not exceed one equivalent. Various aprotic solvents were employed in this Michael addition, see Table 4. The results reveal that ethereal solvents show a lower diastereoselectivity than toluene and dichloromethane. The solvent effect can readily be explained on the basis of the mechanism for the asymmetric proton transfer. In analogy with Scheme 7 the essential intermediates in this asymmetric Michael addition can be pictured as shown in Scheme 8.

Scheme 8 *Mechanistic explanation of the asymmetric Michael addition reaction of lithium thiolates to methacryclic amides* **24b** *and* **24c**



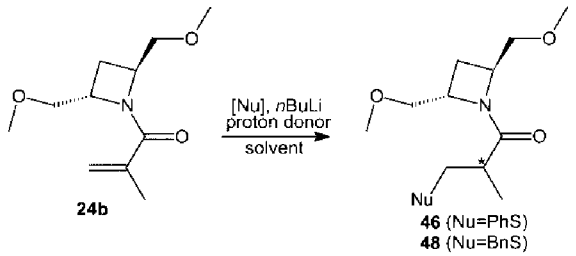
24b (n=1)
24c (n=2)

46 (n=1, R=Ph)
49 (n=2, R=Bn)

In an ethereal solvent there are competing chelating en co-ordinating oxygen atoms which may disturb the defined structure of the essential intermediate. In dichloromethane and toluene such a disturbance cannot occur. It should be mentioned that in dichloromethane the Michael addition is complicated by the formation of some by-products due to reaction of the benzenethiolate ion with the solvent. These by-products have a negative effect on the chromatographic purification of the product. Therefore, toluene is the solvent of choice for this asymmetric conjugate thiolate addition. In the case of benzylthiol the side-reactions with dichloromethane only are of marginal disturbance.

For the sake of completeness various proton donors were tested in the asymmetric Michael addition of thiolates. The results are collected in Table 5.

Table 5 *Various proton donors in the asymmetric Michael addition of thiolates*



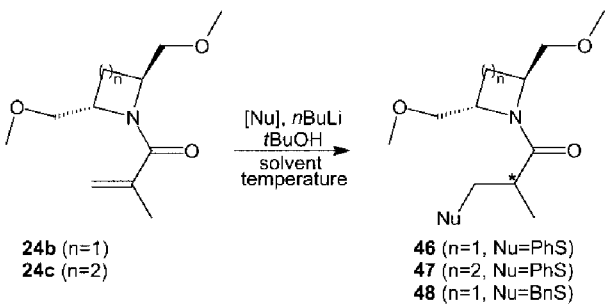
nucleophile	proton donor	solvent	product	*de* (%)[a]
PhSH	*t*BuOH	toluene	**46**	74
PhSH	2,4,6 *t*Bu-phenol	toluene	**46**	65
PhSH	PhSH	toluene	**46**	56
PhSH	*i*Pr$_2$NH	toluene	**46**	64
PhSH	H$_2$O#	toluene	**46**	67
BnSH	*t*BuOH	CH_2Cl_2	**48**	72
BnSH	*i*Pr$_2$NH	CH_2Cl_2	**48**	61
BnSH	H$_2$O#	CH_2Cl_2	**48**	72

added after 1 hour. [a] determined by capillary GC analysis of the crude mixture

The presented data reveal that *tert*-butyl alcohol is clearly the best proton donor. Although di*iso*propylamine and even benzenethiol itself can also be used, the asymmetric outcome is less satisfactory. Unexpectedly, water can also be added after some time, *i.e.* in the work-up procedure, whereby still a quite acceptable diastereoselectivity is achieved.

The experimental conditions for this asymmetric Michael addition were also studied by varying the temperature and the concentration of the reactants. The results are collected in Table 6.

Table 6 *Diastereoselective protonation of enolates, using external proton donors : effect of temperature and concentration*



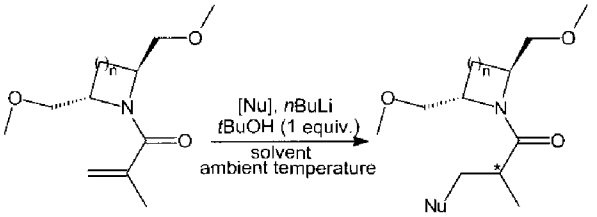
methacrylic amide	nucleophile	solvent	temp.	Conc. (M)	product	*de* (%)[a]	Yield (%)[b]
6b	PhSH	toluene	rt	--	**46**	74	92(25[c])
6b	PhSH	toluene	-78 °C	--	**46**	68	n.d.[d]
6b	BnSH	CH_2Cl_2	rt	--	**48**	72	90(14[c])
6b	BnSH	CH_2Cl_2	-78 °C	--	**48**	62	n.d.[d]
6c	PhSH	toluene	rt	0.04	**47**	65	95(20[c])
6c	PhSH	toluene	rt	0.01	**47**	63	n.d.[d]

[a] determined by capillary GC analysis of the crude mixture. [b] crude yield. [c] isolated yield of major isomer. [d] not determined.

The data clearly indicate that lowering the temperature has a small negative effect on the diastereoselectivity. The concentration effect is negligible.

The experiments described in section **6.3.2** allow the conclusion that the optimal conditions for the conjugate thiolate addition to methacrylic amides **24b** and **24c** are the use of *n*-butyllithium as the base in toluene as the solvent in the presence of *tert*-butyl alcohol as the proton donor. For the sake of clarity these conditions are collected in Table 7.

Table 7 *Optimal conditions for the diastereoselective addition of thiolates to methacrylic amides* **24b** *and* **24c**



24b (n=1)
24c (n=2)

46 (n=1, Nu=PhS)
47 (n=2, Nu=PhS)
48 (n=1, Nu=BnS)
49 (n=2, Nu=BnS)

methacrylic amide	nucleophile	solvent	product	*de* (%)[a]	Yield (%)[b]
24b	PhSH	toluene	**46**	74	92(25[c])
24c	PhSH	toluene	**47**	65	90(14[c])
24b	BnSH	CH_2Cl_2	**48**	72	95(20[c])
24c	BnSH	toluene	**49**	78	96(18[c])

[a] determined by capillary GC analysis of the crude mixture. [b] crude yield.
[c] isolated yield of the major isomer.

It should be noted that in these Michael additions there is no difference between the azetidine and pyrrolidine derived methacrylic amides as far as diastereoselectivity is concerned.

The sense of chirality of the thiolate addition products has not been determined. However, in view of the mechanism of the proton transfer it may be assumed that the same absolute configuration is obtained in this case as was found for the asymmetric addition of thioacids.

6.4 Concluding remarks

The study presented in this chapter shows that an asymmetric Michael addition of sulphur nucleophiles to methacrylic amides derived from chiral small-ring C_2-symmetric amines can be successfully accomplished. For the two types of nucleophiles, *viz.* thiocarboxylic acids and thiols, different experimental conditions are needed.

The diastereoselective conjugate addition of thiocarboxylic acids to methacrylic amide containing 2,4-di(methoxymethyl)azetidine as the chiral auxiliary proceeds with a very high diastereoselectivity. However, when the corresponding 2,5-di(methoxymethyl)pyrrolidine is taken as the chiral auxiliary the Michael addition with thioacetic acid takes place much slower with concurrent unwanted epimerisation and with thiobenzoic acid no reaction occurred at all. Aziridine based chiral auxiliaries were unstable under the conditions of the reaction.

These asymmetric Michael addition to methacrylic amides constitutes a formal chiral synthesis of 3-mercapto-2-methyl-propanoic acid which is a relevant intermediate in the synthesis of the anti-hypertension agent captopril. Mechanistically, a two step process is proposed involving first an activation of the Michael acceptor by carbonyl protonation, followed by Michael addition of the thiocarboxylate to the activated enone system. The asymmetric proton transfer can be rationalised by invoking the initial formed enol in a highly ordered conformation.

The second type of sulphur nucleophiles, *viz.* thiols, that was successfully added to methacrylic amides derived from a C_2-symmetric azetidine and pyrrolidine requires different conditions. This is due to the fact that these thiols are insufficiently acidic to activiate the Michael acceptors. By conversion of the thiols in the corresponding thiolates by reaction with *n*-butyllithium, the Michael addition to both methacrylic amides took place smoothly in an apolar, non-ethereal solvent in the presence of *tert*-butyl alcohol as proton donor. Diastereoselectivities ranging from 65 to 88 % were obtained. Mechanistically, it is assumed that the crucial intermediate is the initially formed lithium enolate which exists in a preferred conformation by chelation *via* the lithium cation. Incorporation of the proton in this species leads to a highly ordered transition state for the asymmetric proton transfer reaction.

In summary, the small-ring C_2-symmetric hetereocyclic amines are efficient chiral auxiliaries in diastereoselective Michael addtion reactions of sulphur nucleophiles, whereby the four-membered ring azetidine derivative shows the best performance.

6.5 Experimental Part

General remarks
Melting points were determined using a Reichert thermopan microscope and are uncorrected. Optical rotations were measured with a Perkin Elmer automatic polarimeter, model 241 MC, using concentrations *c* in g/100 ml at 20 °C in the solvents indicated. ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AC 100 (100 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer. The chemical shift δ is given in ppm relative to the internal standard (TMS for ^{1}H-NMR, $CDCl_3$ for ^{13}C-NMR). IR spectra were recorded on a Perkin Elmer 298 spectrophotometer. The wavenumber ν is listed in cm^{-1}. For (high resolution) mass spectra a double focussing VG7070E mass spectrometer was used. GC-MS were measured using a Varian Saturn II GC-MS by on-column injection (DB-1 column, length 30 m, internal diameter 0.25 mm, film thickness 0.25 μm).

Chemicals
THF was pre-distilled from calcium hydride, and prior to use distilled from sodium/benzophenone. Heptane, hexane, ethyl acetate and dichloromethane were distilled from calcium hydride and stored over 4 Å molsieves. All other reagents were analytical grade and used as such.

Synthesis of the chiral auxiliaries

The chiral auxiliaries **17-19** were prepared according to (slightly modified, see text) literature procedures[23e,f,25].

Synthesis of the chiral methacrylic amides **24a-c**

General procedure

Triethylamine (1.1 equiv) and methacroyl chloride (1 equiv.) were successively added to an ice-cooled solution of the C_2-symmetric hetereocyclic amine. The mixture was stirred for 30 min and then diluted with Et_2O. The mixture was washed with water and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. The methacrylic amide was purified by column chromatography (hexane : ethyl acetate 3:1 (v/v)).

1-[(2*S*,3*S*)-2,3-di(methoxymethyl)aziran-1-yl]-2-methyl-2-propen-1-one **24a**
Aziridine **17** (2.3 g, 17.8 mmol) was treated according to the general procedure, to give 3.4 g (17.1 mmol, 96%) of **24a** as a slightly coloured oil, $[\alpha]_D^{20}$ -49.9 ° (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ : 1.93 (s, 3H, CH_3), 2.79 (dd, *J* = 3.2 Hz, 2H, NC*H*), 3.31 (s, 6H, 2x OCH_3), 3.51 (dd, part of AB J_{AB} = 10.9, ^3J = 3.4 Hz, 2H, CH_2O), 3.63 (dd, part of AB J_{AB} = 10.9, ^3J = 3.7 Hz, 2H, CH_2O), 5.59 (t, 1H *J* = 1.5 Hz, CH_2=C), 5.97 (s, CH_2=C). ^{13}C (100 MHz) δ : 18.1 (CH_3), 38.9

(NCH), 58.5 (OCH_3), 69.9 (OCH_2), 122.8 (H_2C=C), 140.3 (=$CHCH_3$), 178.2 (C=O). IR ($CHCl_3$) ν : 1675 (C=O), 1630 (H_2C=C). *m/z* (CI) (%) : 200(53) [M+1], 130(5), 115(38), 69(51), 41(100).

1-[(2*S*,4*S*)-2,4 di(methoxymethyl)azetan-1-yl]-2-methyl-2-propen-1-one **24b**

The crude azetidine **18** was treated according to the general procedure, to give 3.8 g (17.8 mmol, 44%) of methacrylic amide **24b** as a slightly coloured oil, $[\alpha]_D^{20}$ -105.0 ° (*c* = 1, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ : 1.91 (s, 3H, CH_3), 2.18 (m, 1H, $CHCH_2CH$), 2.36 (m, 1H, $CHCH_2CH$), 3.34 (s, 3H, OCH_3), 3.38 (m, 1H, OCH_2), 3.40 (s, 3H, OCH_3), 3.58 (m, 1H, OCH_2), 3.77 (dd, part of AB, J_{AB} = 10.3 Hz, ^3J = 4.6 Hz, 1H, OCH_2), 4.47 (m, 2H, NC*H*), 5.28 (m, 2H, CH_2=C). ^{13}C (100 MHz) δ : 18.9 ($CHCH_3$), 22.5 ($CHCH_2CH$), 58.4 (OCH_3), 59.1 (NCH), 59.3 (NCH), 61.6 (OCH_3), 72.0 (OCH_2), 72.5 (OCH_2), 117.7 (H_2C=C), 140.4 ($CHCH_3$), 172.0 (C=O). IR ($CHCl_3$) ν : 1650 (C=O). *m/z* (CI) (%) : 214(100) [M+1], 69(68), 41(85).

1-[(2*S*,5*S*)-2,5-di(methoxymethyl)tetrahydro-1*H*-1-pyrrolyl]-2-methyl-2-propen-1-one **24c**

Pyrrolidine **19** (3.0 g, 19 mmol) was treated according to the general procedure, yielding 4.1 g (18 mmol, 95%) of methacrylic amide **24c** as a slightly coloured oil, $[\alpha]_D^{20}$ -65.6 ° (*c* = 1, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ : 1.87-2.18 (m + s, 7H, CH_2CH_2 + $CHCH_3$), 3.21 (m, 2H, OCH_2), 3.31 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 3.42 (dd, part of AB, J_{AB} = 7.1 Hz, 1H, OCH_2), 3.52 (dd, part of AB, J_{AB} = 7.1 Hz, 1H, OCH_2),4.20 (m, 1H, *NCH*), 4.31 (m, 1H, *NCH*), 5.17 (s, 1H, CH_2=C), 5.24 (t, *J* = 1.4 Hz, 1H, CH_2=C). ^{13}C (100 MHz) δ : 14.1 (CH_3), 25.1 (CH_2CH_2), 26.9 (CH_2CH_2), 56.4 (NCH), 58.5 (NCH), 58.8 (2x OCH_3), 71.9 (OCH_2), 73.8 (OCH_2), 115.9 (H_2C=C), 141.8 (=CCH_3), 171.6 (C=O). IR ($CHCl_3$) ν : 1605 (C=O). *m/z* (CI) (%) : 228(100) [M+1], 196(40), 182(43), 150(25), 69(67), 41(93).

Michael addition reactions

Addition of thiocarboxylic acids (general procedure)

To a solution of the methacrylic amide (~ 0.1 M) in dichloromethane, was added one equivalent of thiocarboxylic acid. Then the reaction mixture was stirred at ambient temperature until completion of the reaction (monitored by capillary GC). The reaction mixture was concentrated *in vacuo*, to give the addition product as a mixture of diastereoisomers.

3-[(2*S*,4*S*)-2,4 di(methoxymethyl)-azetan-1-yl]-2-methyl-3-oxopropyl ethanethioate **42**

Methacrylic amide **24b** (213 mg, 1 mmol) was treated according to the general procedure (thioacetic acid, 77 mg) to give 283 mg (98%) of **42** as a mixture of diastereomers (*de* 97%). Column chromatography (heptane : ethyl acetate 1:1 (v/v)) gave 174 mg (60%) of the major isomer as a colourless oil, $[\alpha]_D^{20}$ +12.1 ° (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ : 1.13 (d, ^3J = 6.7 Hz, 3H, $CHCH_3$), 2.02 (m, 1H, $CHCH_2CH$), 2.34 (s, 3H, CH_3C=O), 2.34 (m, 1H, $CHCH_2CH$), 2.66 (m, 1H, $CHCH_3$), 2.93 (dd, part of AB, J_{AB} = 13.3 Hz, ^3J = 6.8 Hz, 1H, CH_2S), 3.04 (dd, part of AB, J_{AB} = 13.3 Hz, ^3J = 5.2 Hz, 1H, CH_2S), 3.36 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.50 (m, 2H, OCH_2), 3.61 (dd, part of AB, J_{AB} = 10.0 Hz, ^3J = 2.6 Hz, 1H, OCH_2), 3.89

(dd, part of AB, J_{AB} = 10.0 Hz, ^3J = 4.8 Hz, 1H, OC*H*$_2$), 4.39 (m, 1H, NC*H*), 4.51 (m, 1H, NC*H*). ^{13}C (100 MHz) δ : 16.9 ($CHCH_3$), 22.0 ($CHCH_2CH$), 30.6 (CH_3C=O), 32.8 (CH_2S), 36.3 ($CHCH_3$), 58.3 (OCH_3), 59.0 (NCH), 59.1 (NCH), 59.8 (OCH_3), 70.7 (OCH_2), 74.9 (OCH_2), 175.0 (C=O), 196.0 (CH_3C=O). IR ($CHCl_3$) ν : 1685 (C=O), 1625 (C=O). *m/z* (CI) (%) : 290(35) [M+1], 214(5) [M-AcSH+1), 100(30), 68(54),43(100).

3-[(2*S*,5*S*)-2,5-di(methoxymethyl)-tetrahydro-1*H*-1-pyrrolyl]-2-methyl-3-oxopropyl ethanethioate **43**

Methacrylic amide **24c** (227 mg, 1 mmol) was treated according to the general procedure (thioacetic acid, 76 mg) to give 288 mg (95%) of **43** as a mixture of diastereomers (*de* 86%). Column chromatography (heptane : ethyl acetate 1:1 (v/v)) gave 145 mg (48%) of the major isomer as a colourless oil, $[a]_D^{20}$ +25.9 ° (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ : 1.20 (d, ^3J = 6.1 Hz, 3H, $CHCH_3$), 1.85-1.99 (m, 3H, CH_2CH_2), 2.12 (m, 1H, CH_2CH_2), 2.34 (s, 3H, CH_3C=O), 2.88-3.02 (m, 3H, $CHCH_3$ + CH_2S), 3.20 (d, ^3J = 6.5 Hz, 2H, OC*H*$_2$), 3.32 (s, 3H, OCH_3), 3.33 (dd, part of AB, J_{AB} = 9.0 Hz, 1H, OC*H*$_2$), 3.35 (s, 3H, OCH_3), 3.59 (dd, part of AB, J_{AB} = 9.2 Hz, ^3J = 3.1 Hz, 1H, OC*H*$_2$), 4.11 (m, 1H, NC*H*), 4.24 (m, 1H, NC*H*). ^{13}C (100 MHz) δ : 17.2 ($CHCH_3$), 25.2 (CH_2CH_2), 27.0 (CH_2CH_2), 30.6 (CH_3C=O), 34.1 (CH_2S), 38.2 ($CHCH_3$), 56.9 (OCH_3), 57.3 (OCH_3), 58.8 (NCH), 59.1 (NCH), 71.1 (OCH_2), 74.5 (OCH_2), 174.2 (C=O), 160.0 (CH_3C=O). IR ($CHCl_3$) ν : 1685 (C=O), 1625 (C=O). *m/z* (CI) (%) : 304(100) [M+1], 114(95), 293(15), 259(25), 161(25), 73(18), 43(37).

3-[(2*S*,4*S*)-2,4 di(methoxymethyl)-azetan-1-yl]-2-methyl-3-oxopropyl benzene carbothioate **44**

Methacrylic amide **24b** (213 mg, 1 mmol) was treated according to the general procedure (thiobenzoic acid, 140 mg) to give 345 mg (98%) of **44** as a mixture of diastereomers (*de* 97%). Column chromatography (heptane : ethyl acetate 1:1 (v/v)) gave 228 mg (65%) of the major isomer as a colourless oil, $[a]_D^{20}$ +16.9 ° (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ : 1.21 (d, ^3J = 6.8 Hz, 3H, $CHCH_3$), 2.02 (m, 1H, $CHCH_2CH$), 2.30 (m, 1H, $CHCH_2CH$), 2.77 (m, 1H, $CHCH_3$), 3.14 (dd, part of AB, J_{AB} = 13.3 Hz, ^3J = 6.4 Hz, 1H, CH_2S), 3.24 (dd, part of AB, J_{AB} = 13.3 Hz, ^3J = 8.3 Hz, 1H, CH_2S), 3.35 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 3.50 (dd, *J* = 4.6 Hz, 2H, OC*H*$_2$), 3.64 (dd, part of AB, J_{AB} = 10.0 Hz, ^3J = 2.7 Hz, 1H, OC*H*$_2$), 3.90 (dd, part of AB, J_{AB} = 10.0 Hz, ^3J = 4.9 Hz, 1H, OC*H*$_2$), 4.41 (m, 1H, NC*H*), 4.50 (m, 1H, NC*H*), 7.46 (m, 2H, C_6H_4), 7.58 (m, 1H, C_6H_4), 7.98 (m, 2H, C_6H_4). ^{13}C (100 MHz) δ : 17.2 ($CHCH_3$), 22.1 ($CHCH_2CH$), 32.7 (CH_2S), 36.5 ($CHCH_3$), 58.3 (NCH), 59.1 (2x OCH_3), 59.9 (NCH), 70.9 (OCH_2), 74.8 (OCH_2), 127.2 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 133.4 ($C_{Ar}H$), 137.1 (C_{Ar}), 175.1 (C=O), 192.1 (C_6H_5C=O). IR ($CHCl_3$) ν : 1705 (C=O), 1630 (C=O). *m/z* (CI) (%) : 352(23) [M+1], 105(100) [C_7H_5O].

Addition of thiols (general procedure, optimal conditions)

A solution of methacrylic amide (1 mmol.), *tert*-butanol (1mmol) and thiol (2 mmol.) in toluene (10 ml) was cooled in ice and stirred under exclusion of oxygen. To this was added

*n*BuLi (1.9 equiv) using a syringe and the mixture was stirred at ambient temperature until completion of the reaction (monitoring by capillary GC). The reaction mixture was then quenchend by the addition of water and the water layer was extracted with dichloromethane (2x). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*, to give the addition products as a mixture of diastereoisomers.

1-[(2*S*,4*S*)-2,4 dimethoxymethyl)-1-azetan-1-yl]-2-methyl-3-(phenylsulfeny;)-1-propanone **46**

Methacrylic amide **24b** (213 mg, 1 mmol) was treated according to the general procedure (benzenethiol, 220 mg) to give 297 mg (92%) of **46** as a mixture of diastereomers (*de* 74%). Column chromatography gave 74 mg (25%) of the major isomer as a colourless oil, $[a]_D^{20}$ -7.0 ° (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ : 1.17 (d, ^3J = 6.7 Hz, 3H, $CHCH_3$), 1.97 (m, 1H, $CHCH_2CH$), 2.27 (m, 1H, $CHCH_2CH$), 2.63 (m, 1H, $CHCH_3$), 2.92 (dd, part of AB, J_{AB} = 13.1 Hz, ^3J = 6.2 Hz, 1H, CH_2S), 3.17 (dd, part of AB, J_{AB} = 13.1 Hz, ^3J = 8.2 Hz, 1H, CH_2S), 3.28 (s, 3H, OCH_3), 3.39 (s + m, 5H, OCH_3 + OCH_2), 3.67 (dd, part of AB, J_{AB} = 10.0 Hz, ^3J = 2.8 Hz, 1H, OCH_2), 3.83 (dd, part of AB, J_{AB} = 10.0 Hz, ^3J = 5.3 Hz, 1H, OCH_2), 4.23 (m, 1H, NC*H*), 4.38 (m, 1H, NC*H*), 7.30 (m, 5H, C_6H_5). ^{13}C (100 MHz) δ : 17.2 ($CHCH_3$), 22.3 ($CHCH_2CH$), 36.0 (CH_2S), 37.8 ($CHCH_3$), 58.2 (OCH_3), 59.0 (NCH), 59.2 (NCH), 59.8 (OCH_3), 71.1 (OCH_2), 75.0 (OCH_2), 126.0 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 129.4 ($C_{Ar}H$), 136.5 (C_{Ar}), 175.2 (*C*=O). IR ($CHCl_3$) ν : 1635 (C=O). *m/z* (CI) (%) : 324(54) [M+1], 214(7) [M-PhSH+1], 151(60), 68(66), 45(100).

1-[(2*S*,5*S*)-2,5 di(methoxymethyl) tetrahydro-1*H*-1-pyrrolyl]-2-methyl-3-(phenylsulfenyl)-1-propanone **47**

Methacrylic amide **24c** (227 mg, 1 mmol) was treated according to the general procedure (benzenethiol, 220 mg) to give 320 mg (95%) of **47** as a mixture of diastereomers (*de* 65%). Column chromatography gave 67 mg (20%) of the major isomer as a colourless oil, $[a]_D^{20}$ +9.0 ° (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ : 1.24 (d, ^3J = 5.6 Hz, 3H, $CHCH_3$), 1.77 (m, 1H, CH_2CH_2), 1.93 (m, 2H, CH_2CH_2), 2.01 (m, 1H, CH_2CH_2), 2.88 (m, 1H, $CHCH_3$), 3.02 (dd, part of AB, J_{AB} = 13.1 Hz, ^3J = 5.5 Hz, 1H, CH_2S), 3.12 (m, 3H, CH_2S + OCH_2), 3.22 (s, 3H, OCH_3), 3.29 (dd, part of AB, J_{AB} = 9.2 Hz, ^3J = 7.8 Hz, 1H, OCH_2), 3.34 (s, 3H, OCH_3), 3.63 (dd, part of AB, J_{AB} = 9.2 Hz, ^3J = 3.1 Hz, 1H, OCH_2), 3.72 (m, 1H, NC*H*), 4.23 (m, 1H, NC*H*), 7.29 (m, 5H, C_6H_5). ^{13}C (100 MHz) δ : 17.9 ($CHCH_3$), 25.1 (CH_2CH_2), 26.8 (CH_2CH_2), 38.0 ($CHCH_3$), 38.9 (CH_2S), 57.0 (OCH_3), 57.2 (OCH_3), 58.8 (NCH), 58.9 (NCH), 71.1 (OCH_2), 74.4 (OCH_2), 126.2 ($C_{Ar}H$), 129.0 ($C_{Ar}H$), 129.1 ($C_{Ar}H$), 136.3 (C_{Ar}), 174.3 (C=O). IR ($CHCl_3$) ν : 1630 (C=O). *m/z* (CI) (%) : 338(12) [M+1], 292(18), 228(7) [M-PhSh+1], 114(100).

3-[(benzylsulfanyl)-1-(2*S*,4*S*)-2,4 di(methoxymethyl)-azetan-1-yl]-2-methyl-1-propanone **48**

Methacrylic amide **24b** (213 mg, 1mmol) was treated according to the general procedure (dichloromethane, benzylmercaptane, 250 mg) to give 303 mg (90%) of **48** as a mixture of diastereomers (*de* 72%). Column chromatography gave 47 mg (14%) of the major isomer as a colourless oil, $[a]_D^{20}$ -40.0 ° (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ : 1.07 (d, ^3J = 6.7

Hz, 3H, CHCH_3), 2.00 (m, 1H, CHCH_2CH), 2.31 (m, 1H, CHCH_2CH), 2.39 (dd, part of AB, J_{AB} = 12.9 Hz, ^3J = 6.0 Hz, 1H, CH_2S), 2.56 (m, 1H, CHCH$_3$), 2.76 (dd, part of AB, J_{AB} = 12.9 Hz, ^3J = 8.3 Hz, 1H, CH_2S), 3.34 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 3.47 (d, J = 4.7 Hz, 2H, OCH_2), 3.67 (dd, part of AB, J_{AB} = 9.9 Hz, ^3J = 2.8 Hz, 1H, 1H, OCH_2), 3.72 (s, 2H, PhCH_2S), 3.84 (dd, part of AB, J_{AB} = 9.9 Hz, ^3J = 5.3 Hz, 1H, 1H, OCH_2), 4.40 (m, 2H, 2x NCH), 7.28 (m, 5H, C$_6H_5$). ^{13}C (100 MHz) δ : 17.5 (CHCH$_3$), 22.3 (CHCH$_2$CH), 35.5 (CH$_2$S), 36.7 (CHCH$_3$), 37.0 (PhCH$_2$S), 58.2 (OCH$_3$), 59.2 (2x NCH), 59.9 (OCH$_3$), 71.1 (OCH$_3$), 75.2 (OCH$_3$), 126.9 (C$_{Ar}$H), 128.8 (C$_{Ar}$H), 128.9 (C$_{Ar}$H), 138.7 (C$_{Ar}$), 175.7 (C=O). IR (CHCl$_3$) ν : 1630 (C=O). *m/z* (CI) (%) : 338(56) [M+1], 214(10) [M-BnSH+1], 114(30), 91(100).

3-[(benzylsulfanyl)-1-(2*S*,5*S*)-2,5 di(methoxymethyl)-tetrahydro-1*H*-1-pyrrolyl]-2-methyl-1-propanone **49**

Methacrylic amide **24c** (227 mg, 1mmol) was treated according to the general procedure (benzylmercaptane, 250 mg) to give 337 mg (96%) of **49** as a mixture of diastereomers (*de* 78%). Column chromatography gave 63 mg (18%) of the major isomer as a colourless oil, $[a]_D^{20}$ -17.7 ° (c = 1, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ : 1.15 (d, ^3J = 6.5 Hz, 3H, CHCH_3), 1.86 (m, 1H, CH_2CH_2), 1.93 (m, 2H, CH_2CH_2), 2.10 (m, 1H, CH_2CH_2), 2.46 (dd, part of AB, J_{AB} = 11.9 Hz, ^3J = 5.1 Hz, 1H, CH_2S), 2.74 (m, 2H, CH_2S + CHCH$_3$), 3.17 (m, 2H, OCH_2), 3.27 (dd, part of AB, J_{AB} = 9.2 Hz, ^3J = 7.8 Hz, 1H, OCH_2), 3.31 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.62 (dd, part of AB, J_{AB} = 9.2 Hz, ^3J = 6.2 Hz, 1H, OCH_2), 3.71 (s, 2H, PhCH_2S), 3.97 (m, 1H, NCH), 4.22 (m, 1H, NCH), 7.28 (m, 5H, C$_6H_5$). ^{13}C (100 MHz) δ : 17.8 (CHCH$_3$), 25.1 (CH$_2$CH$_2$), 26.9 (CH$_2$CH$_2$), 36.9 (CH$_2$S), 37.3 (PhCH$_2$), 38.6 (CHCH$_3$), 56.9 (OCH$_3$), 57.4 (OCH$_3$), 58.8 (NCH), 59.1 (NCH), 71.0 (OCH$_2$), 74.5 (OCH$_2$), 127.0 (C$_{Ar}$H), 128.5 (C$_{Ar}$H), 128.8 (C$_{Ar}$H), 138.4 (C$_{Ar}$), 174.7 (C=O). IR (CHCl$_3$) ν : 1635 (C=O). *m/z* (CI) (%) : 352 (97) [M+1], 320(25), 260(40), 228(8) [M-BnSH+1], 114(100), 91(77).

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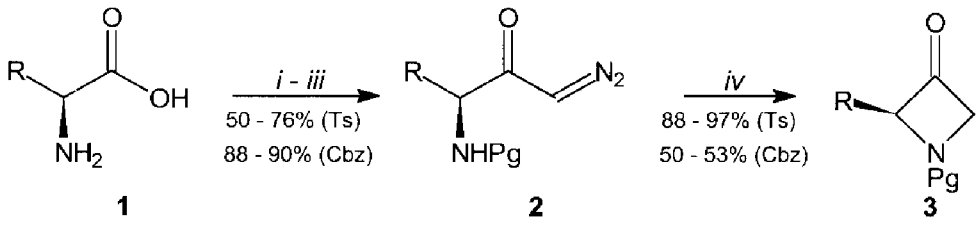
Summary

Azetidines are nitrogen containing, four-membered ring heterocycles, which were prepared for the first time as early as 1888. Since then, these small-ring heterocycles have received relatively little attention and as a consequence these cyclic amines are still rather difficult to prepare, especially in optically pure form. However, the discovery in the last few decades of several naturally occurring functionalised azetidines, many of which posses interesting biological and/or pharmacological activity, has stimulated the interest in this area and research on these strained four-membered ring heterocycles is rapidly increasing.
Functionalised azetidines are also of interest as ligand for (catalytic) asymmetric synthesis. Their increased conformational rigidity as compared to their frequently used five-membered ring analogues, makes them promising asymmetric inductors, potentially more effective than the pyrrolidine derived ligands. Both the synthetic and catalytic aspects of these four-membered ring heterocycles are addressed in this thesis.

The first part of this thesis deals with attempts to develop a new and generally applicable synthetic methodology for the preparation of functionalised azetidines, from inexpensive and readily available starting materials.
In chapter 2 the synthesis of 2-substituted azetidin-3-ones from α-amino acids is described (scheme 1).

Scheme 1 *Synthesis of 2-substituted azetidin-3-ones from α-amino acids*



i) N-protection; *ii*) activation; *iii*) CH_2N_2; *iv*) ringclosure

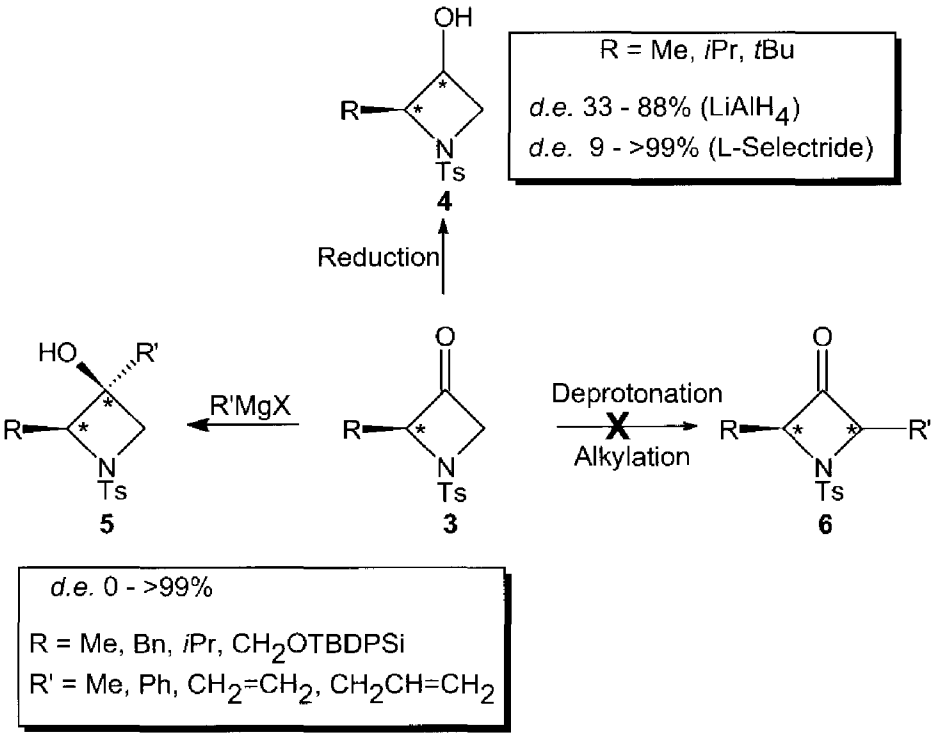
Pg = Ts, R = Me, Bn, *i*Pr, *i*Bu, *s*Bu, *t*Bu, CH_2OTBDPSi
Pg = Cbz, R = *i*Pr, *t*Bu

Protection of the amino function, activation of the carboxylic acid and subsequent treatment with ethereal diazo methane, yields the diazo ketones **2** which in the final step can cyclised to give the desired azetidin-3-ones **3**. The applicability of various

types of protecting groups and their compatibility with several methods of ringclosure is described. The best results were obtained when tosyl protection was combined with a catalytic amount of $BF_3{\cdot}OEt_2$ to effect the ringclosure. In that case the azetidin-3-ones are obtained in almost quantitative yield as practically pure solids.

In chapter 3, the applicability of **3** as chiral synthon for the preparation of substituted azetidines is described (Scheme 2).

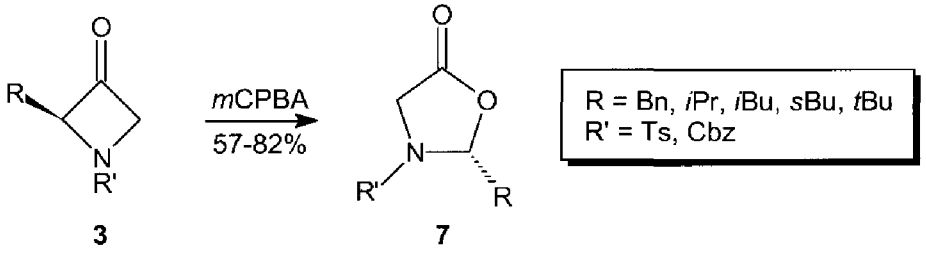
Scheme 2 *Transformations of 2-substituted azetidin-3-ones*



Reduction of the ketone function, an important transformation as many biologically active azetidines are 3-hydroxylated, proceeds with poor (R=Me, *i*Pr) to almost complete (R=*t*Bu) diastereoselectivity. The size of the substituent strongly determines the stereochemistry of the (major) product of the reaction, both in reactions involving product development control ($LiAlH_4$) and steric approach control (L-Selectride). The results obtained are readily explained using generally accepted theories. Grignard reactions with azetidin-3-ones **3** generally proceed with complete stereoselectivity, yielding the thermodynamically most stable *anti* alcohols **5**. Attempts to obtain 2,4-disubstituted azetidin-3-ones **6** *via* a deprotonation -alkylation procedure failed due to the unexpected instability of the azetidinones under basic conditions.

In chapter 4, the Baeyer-Villiger oxidation of azetidin-3-ones **3** to 1,3-oxazolidin-5-ones **7** is described (scheme 3).

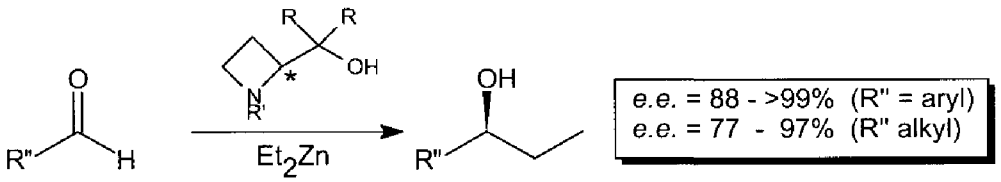
Scheme 3 *Oxidative ring expansion of azetidin-3-ones*



These oxazolidinones can be regarded as chiral glycine equivalents and similar molecules have been used previously for the asymmetric synthesis of mono and di-substituted α-amino acids. The ringexpansion proceeds smoothly, giving the five-membered rings in acceptable to good yields. The use of the products obtained as glycine equivalent was obstructed by the instability of the tosyl protected oxazolidinones under basic conditions. A similar problem was encountered for **3** in chapter 3.

In the two final chapters, the application of azetidines derived ligands for (catalytic) asymmetric synthesis is presented. In chapter 5, amino alcohols derived from *N*-protected azetidine-2-carboxylic esters are successfully used as catalyst in the asymmetric addition of diethylzinc to aldehydes (scheme 4).

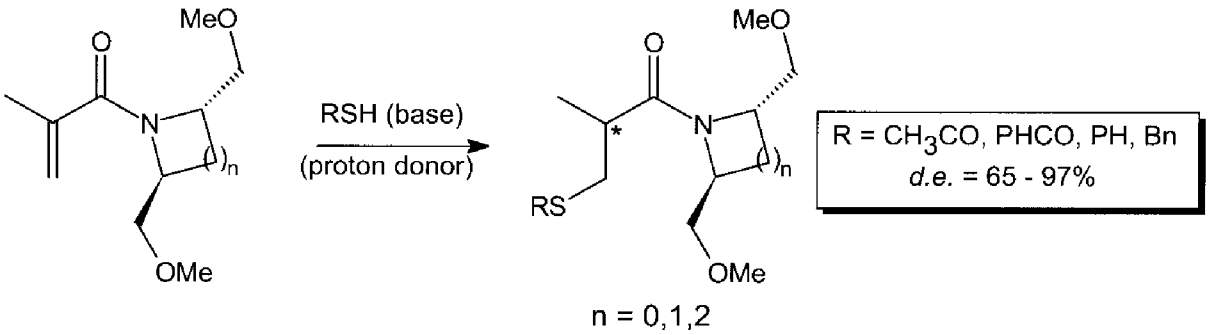
Scheme 4 *Enantioselective addition of diethylzinc to aldehydes, catalysed by azetidine derived amino alcohols.*



The enantioselectivities obtained in the case of aromatic and especially for aliphatic aldehydes, indicate that functionalised azetidines can be excellent catalysts, outperforming the more frequently used five-membered ring analogues. Structural fine-tuning of the ligands reveals that steric bulk of both the alcohol moiety and the nitrogen substituent are crucial for a ligand to be an effective catalyst in enantioselective diethylzinc addition reactions. These observations as well as the stereochemical outcome of the reaction are explained by an adaptation of a previously published transition state model.

In the final chapter, the diastereoselective addition of sulfur nucleophiles to chiral methacryl amides is described (scheme 5).

Scheme 5 *Diastereoselective addition of sulfur nucleophiles to chiral methacryl amides*



The addition of thiocarboxylic acids which is a reaction of industrial importance, proceeds with excellent selectivity (91-97%) in the case of the azetidine derived amide (n=1). When the corresponding pyrrolidine (n=2) is used, the selectivity is somewhat lower for R=CH_3CO (81%) whereas no addition is observed at all for R=PhCO. The unexceptional high induction obtained in this protonation reaction, is explained assuming a directed protonation through bridging of the proton between the methoxymethyl substituent and the prochiral reaction centre *via* hydrogen bonding.

The use of other sulphur nucleophiles requires the use of a strong kinetic base and hence the use of an external proton donor. The selectivities in these cases are considerably lower (65-78%), the optimal conditions involve *n*BuLi as the base, *tert*-butyl alcohol as the proton donor and either toluene or dichloromethane as the solvent at ambient temperature.

The asymmetric Michael addition reactions shown in Scheme 5 are of practical relevance in organic synthesis.

In summary, this thesis describes some novel chemistry of azetidines highlighted by the use of azetidine derived ligands in the enantioselective diethylzinc addition to aldehydes and asymmetric Michael additions using azetidine derived, chiral methacrylic amides.

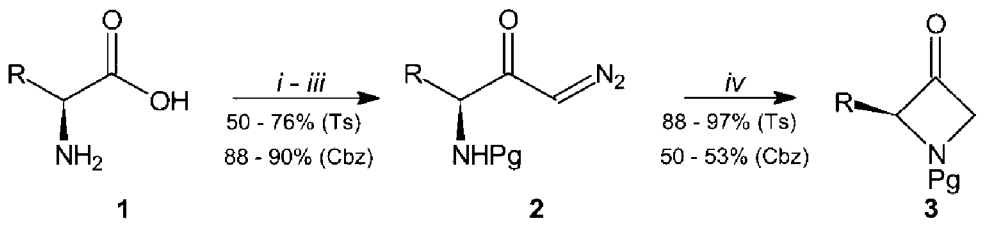
A summary in English and Dutch concludes this thesis.

Samenvatting

Azetidines zijn stikstofhoudende 4-ring heterocycli, die reeds aan het einde van de vorige eeuw voor het eerst werden gesynthetiseerd. Sindsdien heeft deze klasse van kleine-ring heterocycli relatief weinig aandacht gekregen, met als gevolg dat deze cyclische amines nog steeds moeilijk toegankelijk zijn, zeker in een optisch zuivere vorm. Echter, de recente ontdekking van verscheidene natuurlijke gefunctionaliseerde azetidines, waarvan enkele met interessante biologische en/of farmacologische activiteit, heeft een stimulerende werking gehad op de interesse in dit gebied waardoor het onderzoek aan deze gespannen 4-ring heterocycli in een stroomversnelling is gekomen.
Gefunctionaliseerde azetidines zijn ook interessant als ligand voor de (katalytisch) asymmetrische synthese. Hun grotere conformationele rigiditeit in vergelijking met de veel gebruikte gefunctionaliseerde 5-ring analoga, maakt azetidines tot veelbelovende chirale inductoren, die in principe meer effectief kunnen zijn dan de overeenkomstige pyrrolidine liganden. Beide aspecten van deze 4-ring heterocycli worden belicht in dit proefschrift.

Het eerste deel van dit proefschrift, beschrijft de pogingen om een nieuwe en algemeen toepasbare synthese methode te ontwikkelen voor de bereiding van gefunctionaliseerde azetidines, op basis van goedkope en ruim voor handen zijnde uitgangsstoffen.
In hoofdstuk 2 wordt de synthese van 2-gesubstitueerde azetidin-3-onen uitgaande van α-aminozuren beschreven (schema 1).

Schema 1 *Synthese van 2-gesubstitueerde azetidin-3-onen uitgaande van α-aminozuren*



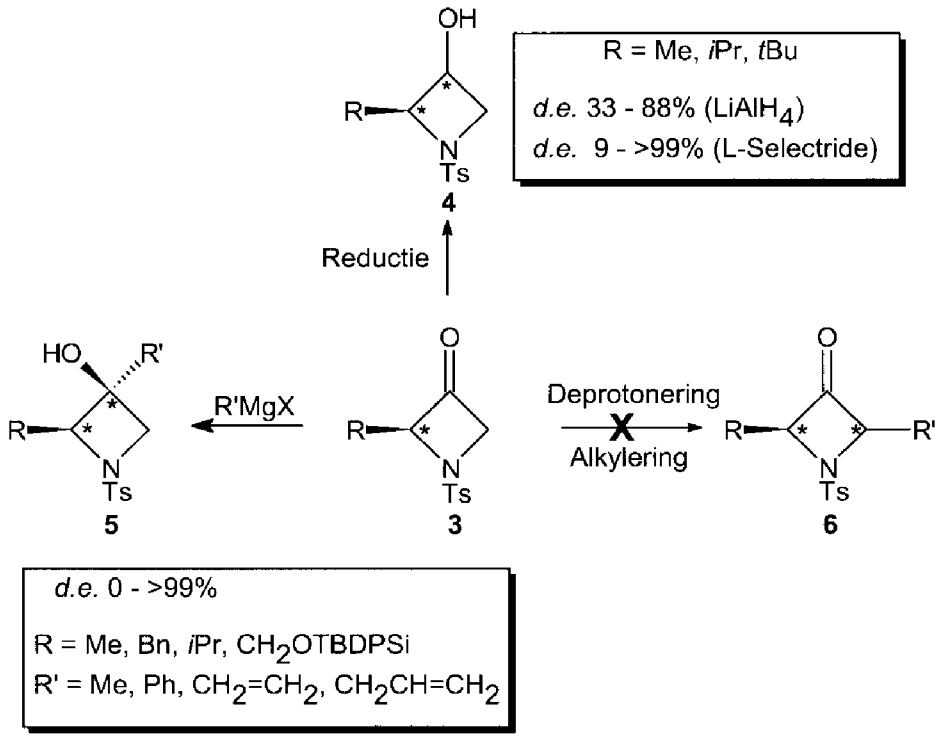
i) N-bescherming; *ii*) activering; *iii*) CH_2N_2; *iv*) ringsluiting

Pg = Ts, R = Me, Bn, *i*Pr, *i*Bu, *s*Bu, *t*Bu, CH_2OTBDPSi
Pg = Cbz, R = *i*Pr, *t*Bu

Bescherming van de amino functie, activering van het carbonzuur en een aansluitende behandeling met diazomethaan, geeft de diazoketonen **2**, welke kunnen

worden ringgesloten tot de gewenste azetidin-3-onen **3**. De toepasbaarheid van diverse beschermgroepen en hun compatibiliteit met verscheidene cyclisatie-methoden is onderzocht. Het beste resultaat wordt verkregen wanneer tosyl bescherming wordt gecombineerd met een katalytische hoeveelheid $BF_3{\cdot}OEt_2$ om de ringsluiting tot stand te brengen. In dat geval worden de azetidinonen verkregen in bijna kwantitatieve opbrengst als vrijwel zuivere vaste stoffen.
In hoofdstuk 3, wordt de toepasbaarheid van **3** als chiraal synthon voor de bereiding van gefunctinaliseerde azetidines belicht (schema 2).

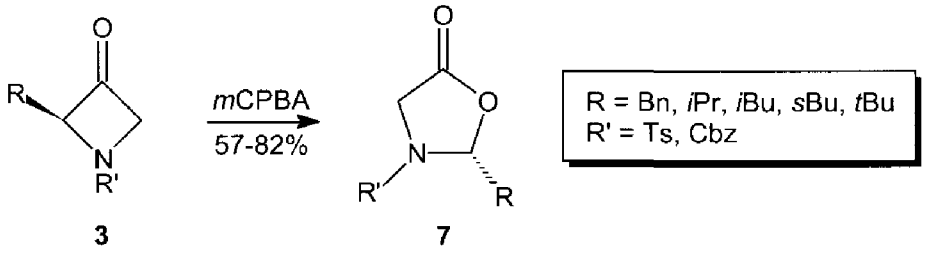
Schema 2 *Transformaties van 2-gesubstitueerde azetidin-3-onen*



Reductie van het keton, een belangrijke omzetting omdat veel biologisch actieve azetidines 3-gehydroxyleerd zijn, verloopt met matige (R=Me, *i*Pr) tot vrijwel complete (R=*t*Bu) diastereoselectiviteit. De sterische bulk van de substituent R bepaalt hierbij in sterke mate de stereochemie van het (hoofd)product, zowel in de $LiAlH_4$ als in de L-Selectride reductie. De verkregen resultaten zijn eenvoudig te verklaren met behulp van algemeen geaccepteerde theorieën. Grignard reacties met azetidin-3-onen verlopen in het algemeen met complete stereoselectiviteit, waarbij de thermodynamisch meest stabiele *anti*-alcoholen **5** als product worden verkregen. Pogingen om 2,4-digesubstitueerde azetidin-3-onen **6** te bereiden *via* een deprotonering-alkylering van **3**, faalden als gevolg van de onverwachte instabiliteit van **3** onder basische condities.

In hoofdstuk 4 wordt de Baeyer-Villiger oxidatie van **3** tot 1,3-oxazolidin-5-onen **7** beschreven (schema 3).

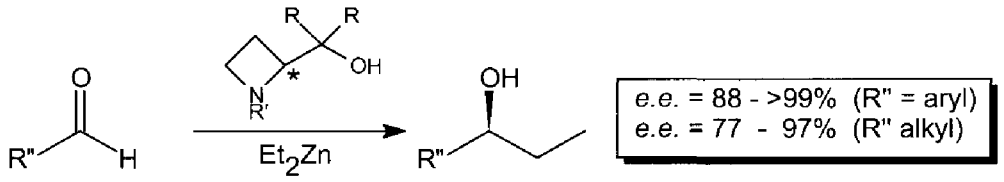
Schema 3 *Oxidatieve ring expansie van azetidin-3-onen*



Deze oxazolidinonen kunnen worden gezien als chiraal glycine equivalent en analoge verbindingen zijn in het verleden als zodanig met succes toegepast in de bereiding van mono- en digesubstitueerde aminozuren. De ringexpansie verloopt soepel, waarbij de 5-ringen in acceptabele tot goede opbrengst worden verkregen. Het gebruik van de verkregen producten als glycine equivalent wordt echter bemoeilijkt door de instabiliteit van tosyl beschermde oxazolidinonen onder basische condities, iets dergelijks is ook waargenomen voor reacties met **3**.

In de laatste twee hoofdstukken, wordt de toepassing van gefunctionaliseerde azetidines als ligand voor (katalytisch) asymmetrische synthese beschreven. In hoofdstuk 5 worden amino alcoholen, afgeleid van N-beschermde azetidine-2-carbonzure esters, met succes gebruikt als katalysator in de asymmetrische additie van diethylzink aan aldehydes (schema 4).

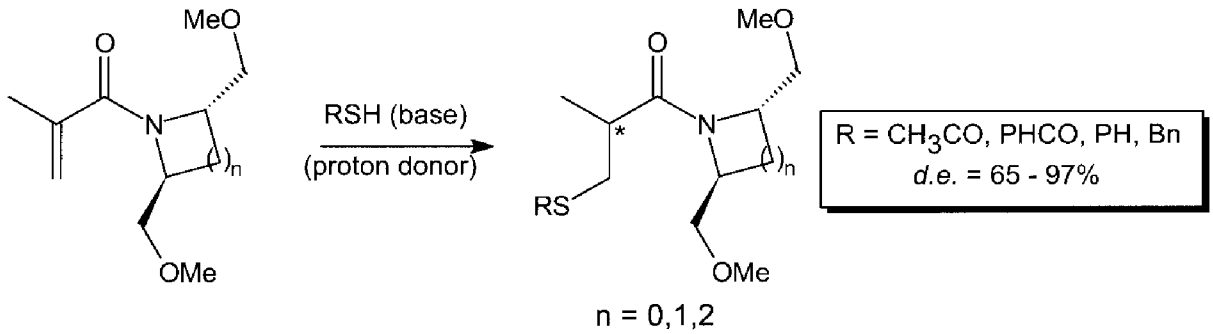
Schema 4 *Enantioselectieve additie van diethylzinkc aan aldehydes, gekatalyseerd door azetidine afgeleide amino alcoholen.*



De verkregen enantioselectiviteiten in het geval van diverse aromatische, maar vooral van alifatische aldehydes, geeft aan dat gefunctionaliseerde azetidines inderdaad uitstekende katalysatoren kunnen zijn en daarbij hun veel gebruikte 5-ring analoga in effectiviteit overtreffen. Structuuroptimalisatie van de liganden laat zien, dat de sterische bulk van zowel de alcohol functie als de stikstof beschermgroep cruciaal is voor de effectiviteit van het ligand. Deze waarneming, alsmede de

stereochemische uitkomst van de reacties, kunnen worden verklaard met behulp van eerder beschreven modellen van de overgangstoestand van de reactie.
In het laatste hoofdstuk, wordt de diastereoselectieve additie van zwavel-nucleofielen aan chirale methacrylamides beschreven (schema 5).

Schema 5 *Diastereoselectieve additie van zwavel-nucleofielen aan chirale methcrylamides*



De additie van thiocarbonzuren, een industrieel relevante reactie, verloopt met uitstekende selectiviteit (91-97%) in het geval van het azetidine afgeleide acrylaat (n=1). Wanneer het overeenkomstige pyrrolidine (n=2) wordt gebruikt is de selectiviteit lager (81%) voor R=CH_3CO terwijl de reactie helemaal niet verloopt voor R=PhCO. De ongewoon hoge asymmetrische inductie die wordt verkregen in de protoneringsreactie kan verklaard worden door complexering van het proton tussen de methoxymethyl substituent en het prochirale reactiecentrum *via* waterstofbrug vorming. Hierdoor wordt het proton selectief van één kant van het enolaat aangeboden.
Het gebruik van andere zwavel-nucleofielen, vereist het gebruik van een sterke, kinetische base en dus het gebruik van een externe protondonor. De selectiviteit in dit geval is aanzienlijk lager (65-78%), waarbij de beste resultaten worden verkregen voor nBuLi als base, *tert*-butylalcohol als protondonor in dichloormethaan dan wel tolueen als oplosmiddel bij kamertemperatuur.
De asymmetrische Michaeladditie reacties die in schema 5 zijn weergegeven, zijn van practische betekenis in de organische synthese.

Samenvattend kan worden gesteld, dat het onderzoek beschreven in dit proefschrift nieuwe chemie op het gebied van de azetidines heeft opgeleverd met als hoogtepunten het gebruik van azetidine bevattende liganden bij de enantioselectieve additie van diethylzink aan aldehyden en de asymmetrische Michaeladditie aan van azetidine afgeleide methacrylamides.

Samenvattingen in het Engels en het Nederlands besluiten dit proefschrift.

List of publications and presentations

A new approach towards optically pure 1,3-oxazolidin-5-ones using a Baeyer-Villiger oxidation of azetidin-3-ones. P.J. Hermsen, P.J.E. Vronen, L. Thijs and B. Zwanenburg, *Eur. J. Org. Chem.*, (submitted)

Enantioselective diethylzinc addition to aldehydes using azetidine derived chiral catalysts, P.J. Hermsen, J.G.O. Cremers, L. Thijs and B. Zwanenburg, *Org. Lett.* (submitted)

*Diastereoslective addition of sulphur nucleophiles to azetidine based chiral methacryl amides.*P.J. Hermsen, L. Thijs and B. Zwanenburg, (in preparation).

Synthesis and exploration of optically active 2-substituted azetidin-3-ones, P.J. Hermsen, P.J.E. Vronen, L. Thijs and B. Zwanenburg.
Poster presentation during '11th International Conference on Organic Synthesis', in Amsterdam, The Netherlands, June 30 - July 4, 1996.

Synthesis and exploration of optically active 2-substituted azetidin-3-ones, P.J. Hermsen, P.J.E. Vronen, L. Thijs and B. Zwanenburg.
Oral communication during the 5th Bologna-Nijmegen Minisymposium 'Bonymi-V' at the University of Camerino, Italy, September 10-17, 1996

Small-ring heterocyclic compounds : versatile intermediates in asymmetric synthesis, P.J. Hermsen, W.A.J. Starmans, L. Thijs and B. Zwanenburg.
Oral communications during the 1997 study tour to RSA, March 12 - April 2, 1997, at the University of Natal (Durban), University of Witwatersrand/ Rand Afrikaans University (Johannesburg) and the University of Potchefstroom.

Synthesis and exploration of optically active 2-substituted azetidin-3-ones, P.J. Hermsen, P.J.E. Vronen, L. Thijs and B. Zwanenburg.
Poster presentations during the 1997 study tour to RSA, March 12 - April 2, 1997, at the University of Cape Town, University of Stellenbosch, University of Natal (Durban), University of Witwatersrand/ Rand Afrikaans University (Johannesburg) and the University of Potchefstroom.

From α-amino acids to functionalised azetidines, P.J. Hermsen, P.J.E. Vronen, L. Thijs and B. Zwanenburg.
Oral communication during the 6th Bologna-Nijmegen Minisymposium 'Bonymi-VI' at the University of Nijmegen, September 14-19, 1998

Stereoselective synthesis via functionalised azetidines, P.J. Hermsen, J.G.O. Cremers, L. Thijs and B. Zwanenburg.
Oral communications during the 1999 study tour to Australia, March 11 - April 7, 1999, at the Australian National University (Canberra) and the Institute for Applied Research (CSIRO), Melbourne.

Stereoselective synthesis via functionalised azetidines, P.J. Hermsen, J.G.O. Cremers, L. Thijs and B. Zwanenburg.
Poster presentations during the 1999 study tour to Australia, March 11 - April 7, 1999 at the University of Queensland and Griffith University (Brisbane), University of New South Wales/ University of Sydney, University of Wollongong, Australian National University (Canberra), Monash University/University of Melbourne and CSIRO (Melbourne).

Asymmetric synthesis using functionalised azetidines. P.J. Hermsen, J.G.O. Cremers, L. Thijs and B. Zwanenburg. Poster presentation during the 1999 European postgraduate poster symposium at Pfizer Central Research, Sandwich, UK, September 22-24, 1999.

Stereoselective synthesis using functionalised azetidines. P.J. Hermsen, J.G.O. Cremers, L. Thijs and B. Zwanenburg. Oral Communication during the anual NWO/CW two-day conference on Design and Synthesis at Lunteren, The Netherlands, October 4-5, 1999.

Curriculum Vitae

De auteur van dit proefschrift werd geboren op 14 mei 1968 te Nijmegen. Na het behalen van het VWO diploma aan de Nijmeegse Scholengemeenschap in 1987, werd in september van dat jaar begonnen met de studie chemische technologie aan de Technische Universiteit te Eindhoven. Twee jaar later werd een overstap gemaakt naar de Katholieke Universiteit Nijmegen, alwaar begonnen werd met de studie scheikunde. Na een uitgebreide hoofdrichting Organische Chemie (Prof. Dr. B. Zwanenburg, Dr. A.J.H. Klunder) en uitgebreide nevenrichting Biochemie (Prof. Dr. W.J. van Venrooij, Dr. G.J.M. Pruijn) werd in februari 1995 het doctoraal examen gehaald.

Van mei 1995 tot mei 1999 was hij als Onderzoeker in Opleiding (OIO) verbonden aan het NSR Center for Molecular Structure, Desingn and Synthesis bij de vakgroep Organische Chemie. Onder leiding van Prof. Dr. B. Zwanenburg verrichte hij het in dit proefschrift beschreven promotieonderzoek.

Sinds 1 november 1999 is de auteur werkzaam als chemicus bij het R&D Center van DSM Fine Chemicals te Venlo.